

# SEARCH REQUEST FORM

Requestor's Name: Rebecca Cook Serial: 0017 Number: 10/05/02  
Date: 3/7/02 Phone: 358 4724 Art Unit: 1614

## Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevant citations, authors keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevant claim(s).

Mr. William Yelle

Please search method of using hydroxyzine  
to treat psoriasis  
ulcers.  
GERD  
gastric  
hypersecretion

Thanks  
Rebecca

BEST AVAILABLE COPY

Point of Contact:  
Toby Port  
Technical Info. Specialist  
CM1 6A04  
703-308-3534

## STAFF USE ONLY

Date completed: 4/3/02

Searcher: 90

Terminal time: 45

Elapsed time: 45

CPU time: 45

Total time: 45

Number of Searches: 45

Number of Databases: 45

### Search Site

STIC

CM-1

Pre-S

### Type of Search

N.A. Sequence

A.A. Sequence

Structure

Bibliographic

### Vendors

IG Suite

STN

Dialog

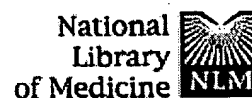
APS

Geninfo

SDC

DARC/Questel

Pubmed Other



PubMed	Nucleotide	Protein	Genome	Structure	PopSet	Taxonomy	OMIM	Bo
Search PubMed	<input checked="" type="checkbox"/> for #4 AND #5				Go	Clear		
Limits		Preview/Index		History	Clipboard	Details		

Field: Title/Abstract

dansoprazole + Boriasis

Display	Abstract	Sort	Save	Text	Clip Add	Order
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Entrez PubMed

☐ 1: J Dermatol 2002 Jan;29(1):23-7

Related Articles, NEW Books, LinkOut

PubMed Services

**Therapeutic effects of antibacterial treatment for intractable skin diseases in Helicobacter pylori-positive Japanese patients.****Sakurane M, Shiotani A, Furukawa F.**

Department of Dermatology, Wakayama Medical University, Japan.

Related Resources

In order to understand the pathogenic relationship between *Helicobacter pylori* (*H. pylori*) and skin diseases, we examined the serum levels of IgG antibody against *H. pylori* and then performed gastroscopic examinations in Japanese patients with chronic skin diseases. These *H. pylori*-positive patients were treated with antibacterial eradication therapy, and therapeutic efficacy was evaluated. A total of 198 patients who were resistant to conventional therapies were randomly selected. They included 50 cases with chronic urticaria, 32 with pruritus cutaneous, 74 with atopic dermatitis, 15 with nummular dermatitis, 17 with prurigo chronica multiformis, 6 with psoriasis vulgaris, and 4 with erythroderma. Positive anti-*H. pylori* antibody was detected in 102 out of these 198 patients; more than half of the ones with chronic urticaria, pruritus cutaneous, nummular dermatitis, and prurigo chronica multiformis had positive antibodies. Gastroscopy was then performed in 48 cases with positive antibodies. Eradication therapy was effective in 60% of the patients with chronic urticaria, in 58% with pruritus cutaneous, in 54% with nummular dermatitis, and in 50% with prurigo chronica multiformis. In chronic skin diseases, persistent infection with *H. pylori* may be an eruption trigger and may cause deterioration of the disease into an intractable and chronic form.

## Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 11837570 [PubMed - indexed for MEDLINE]

Display	Abstract	Sort	Save	Text	Clip Add	Order
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Write to the Help Desk  
NCBI | NLM | NIH  
Department of Health & Human Services  
Freedom of Information Act | Disclaimer

i686-pc-linux-gnu Mar 27 2002 13:44:00

=> file reg; d ide l1; d ide l2; d ide l3  
FILE 'REGISTRY' ENTERED AT 10:48:05 ON 03 APR 2002  
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STRUCTURE FILE UPDATES: 31 MAR 2002 HIGHEST RN 403694-27-9  
DICTIONARY FILE UPDATES: 31 MAR 2002 HIGHEST RN 403694-27-9

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

Please note that search-term pricing does apply when  
conducting SmartSELECT searches.

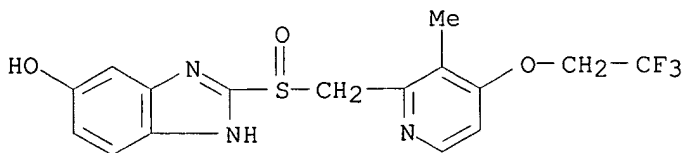
Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES  
for more information. See STN Note 27, Searching Properties in the CAS  
Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

The P indicator for Preparations was not generated for all of the  
CAS Registry Numbers that were added to the H/Z/CA/CAPLUS files between  
12/27/01 and 1/23/02. Use of the P indicator in online and SDI searches  
during this period, either directly appended to a CAS Registry Number  
or by qualifying an L-number with /P, may have yielded incomplete results.  
As of 1/23/02, the situation has been resolved. Also, note that searches  
conducted using the PREP role indicator were not affected.

Customers running searches and/or SDIs in the H/Z/CA/CAPLUS files  
incorporating CAS Registry Numbers with the P indicator between 12/27/01  
and 1/23/02, are encouraged to re-run these strategies. Contact the  
CAS Help Desk at 1-800-848-6533 in North America or 1-614-447-3698,  
worldwide, or send an e-mail to [help@cas.org](mailto:help@cas.org) for further assistance or to  
receive a credit for any duplicate searches.

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS  
RN 131926-98-2 REGISTRY  
CN 1H-Benzimidazol-5-ol, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-  
pyridinyl]methyl]sulfinyl]- (9CI) (CA INDEX NAME)  
OTHER NAMES:  
CN 5-Hydroxylansoprazole  
CN AG 1908  
CN M-VI  
FS 3D CONCORD  
DR 166404-12-2  
MF C16 H14 F3 N3 O3 S  
SR CA  
LC STN Files: ANABSTR, BIOSIS, CA, CAPLUS, TOXCENTER, USPATFULL



514/338  
Q25

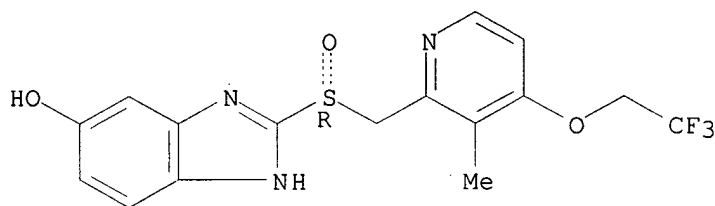
\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

16 REFERENCES IN FILE CA (1967 TO DATE)

17 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS  
RN 220609-28-9 REGISTRY  
CN 1H-Benzimidazol-5-ol, 2-[(R)-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]- (9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C16 H14 F3 N3 O3 S  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry. Rotation (+).



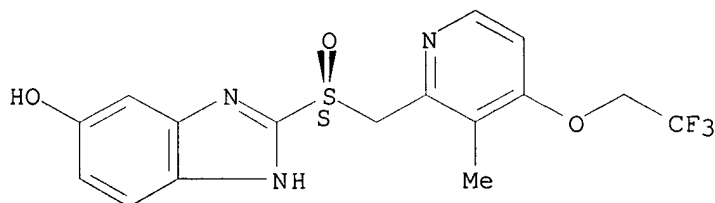
\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

2 REFERENCES IN FILE CA (1967 TO DATE)

2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS  
RN 220609-30-3 REGISTRY  
CN 1H-Benzimidazol-5-ol, 2-[(S)-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]- (9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C16 H14 F3 N3 O3 S  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry. Rotation (-).



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

2 REFERENCES IN FILE CA (1967 TO DATE)  
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> file caplus; d que 120; d que 121; d que 122; d que 123  
FILE 'CAPLUS' ENTERED AT 11:41:25 ON 03 APR 2002  
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FILE COVERS 1907 - 3 Apr 2002 VOL 136 ISS 14  
FILE LAST UPDATED: 2 Apr 2002 (20020402/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the CAS files between 12/27/01 and 1/23/02. As of 1/23/02, the situation has been resolved. Searches and/or SDIs in the H/Z/CA/CAPLUS files incorporating CAS Registry Numbers with the P indicator executed between 12/27/01 and 1/23/02 may be incomplete. See the NEWS message on this topic for more information.

L1	1	SEA FILE=REGISTRY	ABB=ON	PLU=ON	131926-98-2/RN
L2	1	SEA FILE=REGISTRY	ABB=ON	PLU=ON	220609-28-9/RN
L3	1	SEA FILE=REGISTRY	ABB=ON	PLU=ON	220609-30-3/RN
L4	19	SEA FILE=CAPLUS	ABB=ON	PLU=ON	(L1 OR L2 OR L3)
L5	177	SEA FILE=CAPLUS	ABB=ON	PLU=ON	HYDROXYLANSOPRAZOLE OR AG 1908 OR M VI
L6	184	SEA FILE=CAPLUS	ABB=ON	PLU=ON	L4 OR L5
L16	29272	SEA FILE=CAPLUS	ABB=ON	PLU=ON	?ULCER?
L20	2	SEA FILE=CAPLUS	ABB=ON	PLU=ON	L6 AND L16

L1	1	SEA FILE=REGISTRY	ABB=ON	PLU=ON	131926-98-2/RN
L2	1	SEA FILE=REGISTRY	ABB=ON	PLU=ON	220609-28-9/RN
L3	1	SEA FILE=REGISTRY	ABB=ON	PLU=ON	220609-30-3/RN
L4	19	SEA FILE=CAPLUS	ABB=ON	PLU=ON	(L1 OR L2 OR L3)
L5	177	SEA FILE=CAPLUS	ABB=ON	PLU=ON	HYDROXYLANSOPRAZOLE OR AG 1908 OR M VI
L6	184	SEA FILE=CAPLUS	ABB=ON	PLU=ON	L4 OR L5
L17	7962	SEA FILE=CAPLUS	ABB=ON	PLU=ON	?PSORIA?
L21	1	SEA FILE=CAPLUS	ABB=ON	PLU=ON	L6 AND L17

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L1      1 SEA FILE=REGISTRY ABB=ON  PLU=ON  131926-98-2/RN
L2      1 SEA FILE=REGISTRY ABB=ON  PLU=ON  220609-28-9/RN
L3      1 SEA FILE=REGISTRY ABB=ON  PLU=ON  220609-30-3/RN
L4      19 SEA FILE=CAPLUS ABB=ON  PLU=ON  (L1 OR L2 OR L3)
L5      177 SEA FILE=CAPLUS ABB=ON  PLU=ON  HYDROXYLANSOPRAZOLE OR AG 1908
        OR M VI
L6      184 SEA FILE=CAPLUS ABB=ON  PLU=ON  L4 OR L5
L18     1030 SEA FILE=CAPLUS ABB=ON  PLU=ON  (?GASTROESOPH? OR ?ESOPH?) (L)
        REFLUX
L22     2 SEA FILE=CAPLUS ABB=ON  PLU=ON  L6 AND L18

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L1      1 SEA FILE=REGISTRY ABB=ON  PLU=ON  131926-98-2/RN
L2      1 SEA FILE=REGISTRY ABB=ON  PLU=ON  220609-28-9/RN
L3      1 SEA FILE=REGISTRY ABB=ON  PLU=ON  220609-30-3/RN
L4      19 SEA FILE=CAPLUS ABB=ON  PLU=ON  (L1 OR L2 OR L3)
L5      177 SEA FILE=CAPLUS ABB=ON  PLU=ON  HYDROXYLANSOPRAZOLE OR AG 1908
        OR M VI
L6      184 SEA FILE=CAPLUS ABB=ON  PLU=ON  L4 OR L5
L19     20270 SEA FILE=CAPLUS ABB=ON  PLU=ON  ?GASTRIC? (L) ?SECRET?
L23     3 SEA FILE=CAPLUS ABB=ON  PLU=ON  L6 AND L19

```

=> s 120 or 121 or 122 or 123

L54 3 L20 OR L21 OR L22 OR L23

=> file med; d que 137

'MED' IS AN AMBIGUOUS FILE OR CLUSTER NAME

MEDICINE - Medicine and Medical Science Cluster

MEDICONF - Medical Conferences and Events worldwide

MEDLINE - MEDlars onLINE File from 1960 - present

ENTER FILE OR CLUSTER NAME (IGNORE):medline

FILE 'MEDLINE' ENTERED AT 11:41:59 ON 03 APR 2002

FILE LAST UPDATED: 1 APR 2002 (20020401/UP). FILE COVERS 1958 TO DATE.

On April 22, 2001, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE now contains IN-PROCESS records. See HELP CONTENT for details.

MEDLINE is now updated 4 times per week. A new current-awareness alert frequency (EVERYUPDATE) is available. See HELP UPDATE for more information.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2001 vocabulary. Enter HELP THESAURUS for details.

The OLDMEDLINE file segment now contains data from 1958 through 1965. Enter HELP CONTENT for details.

Left, right, and simultaneous left and right truncation are available in the Basic Index. See HELP SFIELDS for details.

THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE SUBSTANCE IDENTIFICATION.

L31 9 SEA FILE=MEDLINE ABB=ON PLU=ON HYDROXYLANSOPRAZOLE OR AG

1908  
L32 15835 SEA FILE=MEDLINE ABB=ON PLU=ON PSORIASIS+NT/CT  
L33 10374 SEA FILE=MEDLINE ABB=ON PLU=ON GASTROESOPHAGEAL REFLUX/CT  
L34 5506 SEA FILE=MEDLINE ABB=ON PLU=ON ULCER/CT  
L35 52474 SEA FILE=MEDLINE ABB=ON PLU=ON PEPTIC ULCER+NT/CT  
L36 6972 SEA FILE=MEDLINE ABB=ON PLU=ON GASTRIC ACID/CT (L) SE/CT  
L37 0 SEA FILE=MEDLINE ABB=ON PLU=ON L31 AND ((L32 OR L33 OR L34  
OR L35 OR L36))

=> file embase; d que 146

FILE 'EMBASE' ENTERED AT 11:42:08 ON 03 APR 2002

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FILE COVERS 1974 TO 28 Mar 2002 (20020328/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

L39 11 SEA FILE=EMBASE ABB=ON PLU=ON HYDROXYLANSOPRAZOLE  
L40 15449 SEA FILE=EMBASE ABB=ON PLU=ON PSORIASIS+NT/CT  
L41 62002 SEA FILE=EMBASE ABB=ON PLU=ON ULCER+NT/CT  
L42 9825 SEA FILE=EMBASE ABB=ON PLU=ON GASTROESOPHAGEAL REFLUX+NT/CT  
L43 2241 SEA FILE=EMBASE ABB=ON PLU=ON STOMACH ACID/CT  
L44 388 SEA FILE=EMBASE ABB=ON PLU=ON ANTIPSORIASIS AGENT/CT  
L45 1847 SEA FILE=EMBASE ABB=ON PLU=ON ANTIULCER AGENT/CT  
L46 0 SEA FILE=EMBASE ABB=ON PLU=ON L39 AND ((L40 OR L41 OR L42 OR  
L43 OR L44 OR L45))

=> file biosis; d que 147

FILE 'BIOSIS' ENTERED AT 11:42:26 ON 03 APR 2002

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FILE COVERS 1969 TO DATE.

CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT  
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 27 March 2002 (20020327/ED)

L47 10 SEA FILE=BIOSIS ABB=ON PLU=ON HYDROXYLANSOPRAZOLE

=> d scan ti

YOU HAVE REQUESTED DATA FROM FILE 'CAPLUS' - CONTINUE? (Y)/N:n

=> d scan ti 147

L47 10 ANSWERS BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

TI **Hydroxylansoprazole** compositions and methods.

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):10

L47 10 ANSWERS BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

TI Pharmacokinetic differences between lansoprazole enantiomers and

contribution of cytochrome P450 isoforms to enantioselective metabolism of lansoprazole in dogs.

- L47 10 ANSWERS BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
TI Genetic polymorphism of CYP2C19 and lansoprazole pharmacokinetics in Japanese subjects.
- L47 10 ANSWERS BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
TI Oxidative metabolism of lansoprazole by human liver cytochromes P450.
- L47 10 ANSWERS BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
TI High-performance liquid chromatographic assay for the simultaneous determination of lansoprazole enantiomers and metabolites in human liver microsomes.
- L47 10 ANSWERS BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
TI Pharmacokinetic differences between lansoprazole enantiomers in rats.
- L47 10 ANSWERS BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
TI Identification of the human P450 enzymes involved in lansoprazole metabolism.
- L47 10 ANSWERS BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
TI Role of CYP3A4 and CYP2C19 in the stereoselective metabolism of lansoprazole by human liver microsomes.
- L47 10 ANSWERS BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
TI Effect of clarithromycin and other macrolides on the sulfoxidation and 5-hydroxylation of lansoprazole in dogs.
- L47 10 ANSWERS BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
TI Metabolic disposition of lansoprazole in relation to the S-mephenytoin 4'-hydroxylation phenotype status.

ALL ANSWERS HAVE BEEN SCANNED

=> S L47 AND COMPOSITIONS/TI  
10761 COMPOSITIONS/TI  
L55 1 L47 AND COMPOSITIONS/TI

=> file wpid; d que l53  
FILE 'WPIDS' ENTERED AT 11:49:12 ON 03 APR 2002  
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FILE LAST UPDATED: 02 APR 2002 <20020402/UP>  
MOST RECENT DERWENT UPDATE 200220 <200220/DW>  
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> SDI'S MAY BE RUN ON EVERY UPDATE OR MONTHLY AS OF JUNE 2001.  
(EVERY UPDATE IS THE DEFAULT). FOR PRICING INFORMATION  
SEE HELP COST <<<

>>> FOR UP-TO-DATE INFORMATION ABOUT THE DERWENT CHEMISTRY  
RESOURCE, PLEASE VISIT  
<http://www.derwent.com/chemistryresource/index.html> <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,  
SEE <http://www.derwent.com/dwpi/updates/dwpicov/index.html> <<<



L48 58 SEA FILE=WPIDS ABB=ON PLU=ON HYDROXYLANSOPRAZOLE OR AG 1908  
OR M VI  
L49 9240 SEA FILE=WPIDS ABB=ON PLU=ON PSORIA? OR ANTIPSORIA?  
L50 197 SEA FILE=WPIDS ABB=ON PLU=ON (GASTROESOPHAGEAL OR GASTRO (L)  
(AESOPH? OR ESOPHAG? OR GASTROAESOPH?)) (L) REFLUX OR GERD  
L51 14958 SEA FILE=WPIDS ABB=ON PLU=ON ULCER? OR ANTIULCER?  
L52 2361 SEA FILE=WPIDS ABB=ON PLU=ON GASTRIC (3A) (SECRET? OR  
HYPERSECRET?)  
L53 2 SEA FILE=WPIDS ABB=ON PLU=ON L48 AND ((L49 OR L50 OR L51 OR  
L52))

=> DUP REM L54 L55 L53

FILE 'CAPLUS' ENTERED AT 11:49:29 ON 03 APR 2002  
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FILE 'WPIDS' ENTERED AT 11:49:29 ON 03 APR 2002  
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PROCESSING COMPLETED FOR L54  
PROCESSING COMPLETED FOR L55  
PROCESSING COMPLETED FOR L53

L56 5 DUP REM L54 L55 L53 (1 DUPLICATE REMOVED)  
ANSWERS '1-3' FROM FILE CAPLUS  
ANSWER '4' FROM FILE BIOSIS  
ANSWER '5' FROM FILE WPIDS

=> d ibib ab l56 1-5; file home

L56 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1  
ACCESSION NUMBER: 2000:84622 CAPLUS  
DOCUMENT NUMBER: 132:141954  
TITLE: Pharmaceutical compositions comprising  
**hydroxylansoprazole** for **ulcer**  
treatment  
INVENTOR(S): Yelle, William E.  
PATENT ASSIGNEE(S): Sepracor Inc., USA  
SOURCE: PCT Int. Appl., 18 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000004904	A1	20000203	WO 1999-US16322	19990719
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
AU 9952182	A1	20000214	AU 1999-52182	19990719



studies with metabolites of lansoprazole revealed that three metabolites were more potent inhibitors of testosterone synthesis than the parent drug, two of them being at least 10 times more potent. These metabolites are present in rats at substantial levels but are undetectable in humans. The lack of induction of Leydig cells tumors in mice, lower sensitivity of primate Leydig cells, and the absence of testosterone synthesis-inhibiting metabolites in man suggest that Leydig cell tumors found in rats represent a species-specific sensitivity and does not imply a risk for clin. use in man.

L56 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1991:421996 CAPLUS  
DOCUMENT NUMBER: 115:21996  
TITLE: Effects of AG-1749 (lansoprazole) and its metabolites on acid secretion and experimental **ulcers**  
AUTHOR(S): Inatomi, Nobuhiro; Nagaya, Hideaki; Ishisaka, Yoichi; Satoh, Hiroshi  
CORPORATE SOURCE: Res. Dev. Div., Takeda Chem. Ind., Ltd., Japan  
SOURCE: Yakuri to Chiryo (1991), 19(2), 477-86  
CODEN: YACHDS; ISSN: 0386-3603  
DOCUMENT TYPE: Journal  
LANGUAGE: Japanese

AB The effects of AG-1749 (I) and its metabolites on canine microsomal (H<sup>+</sup>+K<sup>+</sup>)-ATPase, acid formation in canine **gastric** parietal cells, **gastric acid secretion** in rats and dogs, and exptl. stomach and duodenal **ulcers** in rats were studied. AG-1749 inhibited (H<sup>+</sup>+K<sup>+</sup>)-ATPase activity in canine microsomes and acid formation in canine parietal cells stimulated by dibutyryl cAMP in a concn.-dependent manner. The IC<sub>50</sub> values were 6.3 and 0.09 .mu.M, resp. The hydroxy metabolite inhibited (H<sup>+</sup>+K<sup>+</sup>)-ATPase activity with IC<sub>50</sub> = 3 .mu.M, but it did not inhibit acid formation in isolated parietal cells. The sulfonyl metabolite affected neither microsomal (H<sup>+</sup>+K<sup>+</sup>)-ATPase activity nor acid formation in parietal cells. AG-1749 inhibited histamine-stimulated acid **secretion** in dogs and rats; the ID<sub>50</sub> values were 0.14 mg/kg i.v. and 0.4 mg/kg i.p., resp. Neither metabolite inhibited acid **secretion** in dogs and rats at 1 mg/kg i.v. and 10 mg/kg i.p. AG-1749 inhibited **reflux esophagitis**, water-immersion stress-induced **gastric** lesions, and mepirizole-induced duodenal **ulcers** in rats in a dose-dependent manner; ID<sub>50</sub> values were 0.4, 0.7, and <0.1 mg/kg, i.p., resp. The metabolites barely inhibited the exptl. **ulcers**. The **antisecretory** and **antiulcer** effects by AG-1749 are exerted mainly by AG-1749 itself and not by its 2 metabolites.

L56 ANSWER 4 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2002:144673 BIOSIS  
DOCUMENT NUMBER: PREV200200144673  
TITLE: **Hydroxylansoprazole compositions** and methods.  
AUTHOR(S): Yelle, William E.  
ASSIGNEE: Sepracor Inc.  
PATENT INFORMATION: US 6335351 January 01, 2002  
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Jan. 1, 2002) Vol. 1254, No. 1, pp. No  
Pagination. <http://www.uspto.gov/web/menu/patdata.html>.  
e-file.  
ISSN: 0098-1133.  
DOCUMENT TYPE: Patent  
LANGUAGE: English

AB Methods and compositions are disclosed utilizing **hydroxylansoprazole** for the treatment of ulcers in humans.

**Hydroxylansoprazole** exhibits a lessened liability toward drug-drug interactions than lansoprazole and a more predictable dosing regimen than lansoprazole. **Hydroxylansoprazole** is also usefull for the treatment of gastroesophageal reflux and other conditions related to gastric hypersecretion such as Zollinger-Ellison Syndrome.

L56 ANSWER 5 OF 5 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD  
 ACCESSION NUMBER: 2000-628241 [60] WPIDS  
 DOC. NO. CPI: C2000-188228  
 TITLE: New indolinone derivatives are protein kinase inhibitors used for treating e.g. cardiovascular, dermatological and immune disorders and cancer.  
 DERWENT CLASS: B02  
 INVENTOR(S): HARRIS, G D; LIANG, C; MCMAHON, G; MILLER, T A; SHIRAZIAN, S; SUN, L; TANG, P C; WEI, C C; XIAOYUAN, L  
 PATENT ASSIGNEE(S): (SUGE-N) SUGEN INC  
 COUNTRY COUNT: 93  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000056709	A1	20000928	(200060)*	EN	241
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000037700	A	20001009	(200103)		
EP 1165513	A1	20020102	(200209)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000056709	A1	WO 2000-US7704	20000322
AU 2000037700	A	AU 2000-37700	20000322
EP 1165513	A1	EP 2000-916622	20000322
		WO 2000-US7704	20000322

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000037700	A Based on	WO 200056709
EP 1165513	A1 Based on	WO 200056709

PRIORITY APPLN. INFO: US 1999-132243P 19990503; US 1999-125945P  
 19990324; US 1999-127863P 19990405; US  
 1999-131192P 19990426

AB WO 200056709 A UPAB: 20001123  
 NOVELTY - Indolinone derivatives (I) are new.  
 DETAILED DESCRIPTION - Indolinone derivatives of formula (I) and their salts are new.  
 n, m = 0 or 1;  
 when n is 1, then:  
 A, B, D, E, F = C or N,  
 provided that they are not all N and when A, B, D, E or F is N, then:  
 R4-R8 = absent;

when m is 1, then:  
G, H, J, K, L = C or N,  
provided that 1-3 of them are N and when G, H, J, K or L is N, then:  
R9-R13 = absent;  
when n is 0, then:  
A = C or N;  
B, F = C, N, NH, O or S and  
E = C, N, O or S,  
provided that when B or F is NH, the other is not NH and provided  
that no more than 1 of B, E and F is O or S and provided that at least one  
of A, B, E or F is a heteroatom;

when m is 0, then:  
G = C or N and  
H, K, L = C, N, NH, O or S,  
provided that when H or L is NH, the other is not NH and K is C, N, O  
or S and provided that no more than one of H, K or L is O or S and  
provided that at least one of G, H, K or L is a heteroatom;

R1-R13 = H, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl,  
heteroaryl, heteroalicyclic, OH, alkoxy, mercapto, alkylthio, aryloxy,  
arylthio, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, CO, C-carboxy,  
O-carboxy, carboxyalkyl, CN, NO<sub>2</sub>, halo, O-carbamyl, N-carbamyl, C-amido,  
N-amido or NR14R15 or

R4 + R5, R5 + R6, R6 + R7 or R8 + R8 (sic) = 5- or 6-membered aryl or  
heteroaryl and

R14, R15 = H, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl,  
CO or sulfonyl or

R14 + R15 = 5- or 6-membered ring.

INDEPENDENT CLAIMS are included for the following:

(1) indolinone derivatives of formula (II)-(V) and their salts;  
(2) an indolinone compound formed by reacting one of 20 specified  
ketones e.g. of formula (VI) with one of 12 specified oxindole compounds  
e.g. 1,3-dihydroindol-2-one and

(3) identifying indolinone compounds that modulate the function of  
protein kinase which comprises contacting cells expressing protein kinase  
with (I)-(V) and monitoring an effect upon the cells.

In (II):

n = 0 or 1;

when p is 1, then:

M, Q, T, Y, V = C or N,

provided that when M, Q, T, Y or V is N, then R20-R24 are absent;

when p is 0, then:

M, Q, Y, V = C, N, O or S,

provided that when M, Q, Y or V is O or S, then R20-R24 are absent;

R16-R24 = H, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl,  
heteroaryl, heterocyclyl, OH, alkoxy, mercapto, alkylthio, aryloxy,  
sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, CO, NO<sub>2</sub>, halo,  
O-carbamyl, N-carbamyl, C-amido, N-amido or NR25R26 or

R20 + R21, R21 + R22, R23 + R23 (sic) or R23 + R24 = 5- or 6-  
membered aryl or heteroaryl;

R25, R26 = H, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl,  
carbonyl or sulfonyl and

R25 + R26 = 5- or 6- membered heteroalicyclic ring;

In (III):

R27 = alkyl, aromatic or heteroaromatic ring or aliphatic or  
heteroaliphatic ring (all optionally substituted);

R28-R34 = H or alkyl, aromatic or heteroaromatic ring or aliphatic or  
heteroaliphatic ring (all optionally substituted), (X1)n1-NX2X3, NO<sub>2</sub>,  
halo, trihalomethyl, (X4)n4-CO-X5, (X6)n6-COOH, (X7)n7-COOX8, (X9)n9-OH,  
(X10)n10-O-X11, (X12)n12-NHCOX13, (X14)n14-CONX15X16, (X17)n17-SO2NX18X19,  
(X20)n20-COH, (X21)n21-SO2-X22 or (X23)n23-SH;

X1, X6-X8 = alkyl or 5- or 6- membered aromatic, heteroaromatic or

aliphatic ring;

X2, X3 = H, alkyl or 5- or 6- membered aromatic, heteroaromatic or aliphatic ring;

X4, X5, X9-X11, X17, X20 = alkyl or 5- or 6- membered aromatic, heteroaromatic or aliphatic ring (all optionally substituted);

X12-X16 = alkyl, OH or 5- or 6- membered aromatic, heteroaromatic or aliphatic ring (optionally substituted);

X18, X19 = H or alkyl or 5- or 6- membered aromatic, heteroaromatic or aliphatic ring (optionally substituted) or

X18 + X19 = 5- or 6- membered aliphatic or heteroaliphatic ring (optionally substituted);

n1, n4, n6, n7, n9, n10, n12, n14, n20, n21, n23, n24 = 0 or 1 and n17 = 0-2.

In (IV) and (V):

R1, R2, R7 = H or alkyl or aromatic or heteroaromatic ring (all optionally substituted);

R3 = CH<sub>2</sub>CH<sub>2</sub>-O-R;

R = H or alkyl or aromatic or heteroaromatic ring (all optionally substituted) or C(E)NX<sub>15</sub>X<sub>16</sub>;

X15, X16 = H, alkyl, OH, SO<sub>2</sub>-X<sub>22</sub> or 5- or 6-membered aromatic, heteroaromatic, aliphatic or heteroaliphatic ring (all optionally substituted);

E = O or S;

R4-R6 = H;

Z = 5-10 membered mono- or bi-cyclic aromatic or heteroaromatic ring (optionally substituted) and

R35, R37-R41 = not defined.

In (VI):

R1 = alkyl, aromatic or heteroaromatic ring or aliphatic or heteroaliphatic ring (all optionally substituted).

ACTIVITY - Cytostatic; immunostimulant; antiproliferative; cardiant; antiinflammatory, antipsoriatic; dermatological; antiarthritic; antiarteriosclerotic; antidiabetic.

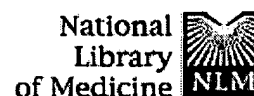
MECHANISM OF ACTION - Protein kinase inhibitor; receptor protein tyrosine kinase inhibitor; cellular tyrosine kinase inhibitor; serine threonine kinase inhibitor; in cell signal transduction pathway modulator; protein phosphatase inhibitor.

3-(4-(3-dimethylaminopropyl)-3,5-dimethyl-1H-pyrrol-2-ylmethylene)-6-pyridin-3-yl-1,3-dihydroindol-2-one exhibited IC<sub>50</sub> values (in  $\mu$ M) of 16.76, 0.02 and 12.08 against Her-kinase, bio PDGFr and bio EGFr, respectively.

USE - Used for treating cancer, immunological, hyperproliferation, cardiovascular and inflammation disorders, restenosis, fibrosis, psoriasis, osteoarthritis, rheumatoid arthritis, atherosclerosis, diabetes, renal disease, angiogenesis and diseases related to PYK-2 protein.

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☐ 1: Postgrad Med 2001 Oct;Spec No:24-35

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## Proton pump inhibition. An effective, safe approach to GERD management.

Berardi RR.

University of Michigan College of Pharmacy, Department of Pharmacy, University of Michigan Health System, Ann Arbor, USA. rberardi@umich.edu

Related Resources

Prescribed worldwide to treat gastroesophageal reflux disease (GERD), the proton pump inhibitors (PPIs) not only relieve acid reflux-related symptoms more rapidly than standard-dose or high-dose histamine<sub>2</sub> receptor antagonists but also accelerate the rate of esophageal healing. Five PPIs--omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole--are currently labeled by the Food and Drug Administration. These agents share a common mechanism of action and rarely exhibit clinically important interactions with other hepatically metabolized medications or pH-dependent drugs. Except for lingering concern about their long-term use in *Helicobacter pylori*-positive patients, the PPIs produce relatively few adverse effects when administered for the short or long term. Because primary care physicians are generally the first to treat patients with GERD, they may find it helpful to expand their knowledge of the pharmacologic effects of the PPIs. With an eye toward this end, Dr Berardi presents a cogent overview of PPI pharmacodynamics, pharmacokinetics, efficacy, drug interactions, and safety.

### Publication Types:

- Review
- Review, Tutorial

PMID: 11868428 [PubMed - indexed for MEDLINE]

☐ 2: Clin Ther 2001 Aug;23(8):1130-44; discussion 1129

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ELSEVIER SCIENCE  
FULL-TEXT ARTICLE

## Dyspepsia: challenges in diagnosis and selection of treatment.

Robinson M.

University of Oklahoma College of Medicine, Oklahoma Foundation for Digestive Research, Oklahoma City 73104-5022, USA. malcolm-robinson@ouhsc.edu

**BACKGROUND:** Despite considerable study, the pathophysiology of dyspepsia remains obscure. This and other factors have impeded development of precise and effective treatment strategies. **OBJECTIVE:** This paper provides a brief review of the clinical syndrome of dyspepsia and its pathophysiology, symptoms, diagnosis, and treatment. **METHODS:** To identify articles for inclusion in this review, a search of MEDLINE was conducted using the key word dyspepsia. Because the literature on this topic is voluminous and duplicative, the search was limited primarily to literature from the last decade and to articles concerning dyspepsia in adults. **RESULTS:** The symptoms of dyspepsia, which may include epigastric pain, heartburn, bloating, and early satiety, defy diagnosis in as many as 50% of patients, even after endoscopy and other appropriate studies. In the other half of patients, such causative disorders as gastroesophageal reflux disease (GERD), peptic ulcer disease, cholecystitis, pancreatitis, and gastric cancer may be diagnosed. Despite controversy regarding the selection of therapy, empiric treatment is common for apparent idiopathic dyspepsia. Histamine<sub>2</sub>-receptor antagonists, proton pump inhibitors (PPIs), promotility agents, and coating agents have all been used as empiric therapy for dyspeptic symptoms. With empiric treatment, subsequent management is directed by the therapeutic

response. In the absence of a definitive diagnosis, treatment is usually selected on the basis of the type and severity of symptoms, a thorough history and physical examination, and factors such as age and the presence of *Helicobacter pylori* infection. Five PPIs are currently available--lansoprazole, omeprazole, rabeprazole, pantoprazole, and esomeprazole--all with established efficacy in GERD and other acid-mediated disorders. The PPIs can be expected to be useful in certain patients with dyspepsia, and may be prescribed for patients who are found to respond to potent antisecretory therapy. Patients' concern about their symptoms, practical considerations, and restrictions imposed by managed care organizations may all affect the choice between empiric therapy and early endoscopy in patients with dyspepsia. **CONCLUSIONS:** Despite the variety of therapeutic options available for the symptoms of dyspepsia, the many presentations of this condition and the uncertainty of the response to the currently available therapeutic options continue to pose a substantial clinical challenge.

Publication Types:

- Review
- Review, Tutorial

PMID: 11558854 [PubMed - indexed for MEDLINE]

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☐ 3: Expert Opin Pharmacother 2000 Sep;1(6):1171-94

Related Articles, **NEW** Books, LinkOut

**Proton pump inhibitors in the treatment of gastro-oesophageal reflux disease.**

Tolman KG, Chandramouli J, Fang JC.

Department of Internal Medicine and Pharmacy, University of Utah School of Medicine, Salt Lake City, Utah 84132, USA.

Gastro-oesophageal reflux disease (GERD) is the most common peptic acid disease in the western world and is the commonest indication for acid suppression therapy. Major advances have been made over the past 30 years in the understanding of lower oesophageal sphincter function and the mechanism of acid secretion. Developments in surgical and pharmacological therapy have paralleled these advances. Pharmacotherapy for GERD has evolved from antacids to H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) to prokinetics to proton pump inhibitors (PPIs). The H<sub>2</sub>RAs, while modestly effective in symptom relief and healing of GERD, are limited by pharmacological tolerance. The prokinetics (metoclopramide and cisapride) are limited by low efficacy, pharmacological tolerance and toxicity. The PPIs have emerged as the most effective therapy for symptom relief, healing and long-term maintenance. They have also proved to be remarkably safe and cost-effective in long-term therapy. This review evaluates the pharmacology, efficacy, tolerability, safety and cost-effectiveness of the four currently available PPIs, lansoprazole, omeprazole, pantoprazole and rabeprazole, in the treatment of GERD.

Publication Types:

- Review
- Review, Academic

PMID: 11249486 [PubMed - indexed for MEDLINE]

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☐ 4: Am J Health Syst Pharm 1999 Dec 1;56(23 Suppl 4):S18-21

Related Articles, **NEW** Books, LinkOut

Erratum in:

- Am J Health Syst Pharm 2000 Apr 1;57(7):699

**Comparison of 24-hour intragastric pH using four liquid formulations of lansoprazole and omeprazole.**

Sharma VK.

Division of Gastroenterology, University of Arkansas for Medical Sciences, Little Rock 72205-7199, USA. sharmavirenderk@exchange.uams.edu

The results of previous studies evaluating the effect of four liquid formulations of proton-pump inhibitors on 24-hour intragastric pH are described. Patients with a gastrostomy who were resident in a Veterans Affairs medical center or its affiliated nursing home were eligible for enrollment in one of four open-label studies in which each patient served as his own control. Patients underwent 24-hour intragastric pH studies before and



after receiving seven consecutive days of one of the following liquid formulations of a proton-pump inhibitor administered once daily: omeprazole granules 20 mg in orange juice, lansoprazole granules 30 mg in orange juice, simplified omeprazole suspension 20 mg, and simplified lansoprazole suspension 30 mg. The suspensions were prepared with 10 mL of 8.4% sodium bicarbonate solution. Mean intragastric pH was measured, as was the time pH stayed above 3.0 and 4.0 during the 24-hour period. Six to 14 patients participated in each study. The mean posttreatment pH was 4.9+/-0.8, 4.7+/-0.6, 4.1+/-1.5, and 5.1+/-1.1 for omeprazole granules in orange juice, lansoprazole granules in orange juice, simplified omeprazole suspension, and simplified lansoprazole suspension, respectively. Both drugs in orange juice maintained pH above 4.0 longer than 14 hours and above 3.0 for close to 20 hours, which are the levels deemed optimal for healing erosive esophagitis and duodenal ulcers, respectively. Simplified lansoprazole suspension maintained pH above those thresholds for the optimal times, but simplified omeprazole suspension did not (20 and 15 hr above 3.0, 17 and 12 hr above 4.0 for lansoprazole and omeprazole, respectively). Further development of liquid formulations of proton-pump inhibitors may have important implications for the treatment of acid-related diseases in patients, including children, who are unable to swallow capsules.

## Publication Types:

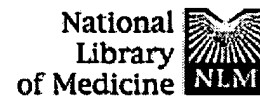
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☐ 1: Nippon Rinsho 2002 Jan;60(1):174-81

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### [Progress of tailor-made treatment of peptic ulcer]

[Article in Japanese]

Aoyama N, Shirasaka D, Okumura K.

Department of Endoscopy, Kobe University School of Medicine.

We previously reported that a comparative pharmacokinetic study with each PPI was designed as an open, randomized, and crossover study of 18 Japanese healthy volunteers who were classified into the homozygous, heterozygous extensive metabolizer and the poor metabolizer based on the CYP2C19 genotype. With at least 1 week washout period between treatments. Plasma concentrations of PPIs and their metabolites were monitored until 12 h after medication. Pharmacokinetic profiles of omeprazole and lansoprazole were well correlated with the CYP2C19 genotype. The heterozygous extensive metabolizer was slightly different from the homozygote, but there was no statistically significant difference. The CYP2C19 genotype dependence found for lansoprazole was not obvious compared with omeprazole. As for rabeprazole, the pharmacokinetic profile was independent of the CYP2C19 genotype. CYP2C19 genotyping can provide a new strategy to choose an optimal regimen, and this genotyping is especially useful for Japanese, as the frequency of poor metabolizers is five times greater than that found among Caucasians.

#### Publication Types:

- Review
- Review, Tutorial

PMID: 11808330 [PubMed - indexed for MEDLINE]

☐ 2: Drugs 2001;61(15):2327-56

[Related Articles](#), [NEW Books](#), [LinkOut](#)

### Rabeprazole: an update of its use in acid-related disorders.

Carswell CJ, Goa KL.

Adis International Limited, Auckland, New Zealand. demail@adis.co.nz

Rabeprazole is an inhibitor of the gastric proton pump. It causes dose-dependent inhibition of acid secretion. In 8-week studies, among patients with gastro-oesophageal reflux disease (GORD), rabeprazole 20 mg/day or 10mg twice daily was as effective as omeprazole and superior to ranitidine in the healing of GORD. Symptom relief with rabeprazole was superior to that provided by placebo and ranitidine and similar to omeprazole. In long-term trials rabeprazole 10 mg/day was similar to omeprazole 20 mg/day in a 2-year study and superior to placebo in 1-year studies, in both the maintenance of healing and prevention of symptoms in patients with healed GORD. In nonerosive GORD, 4-week studies have shown rabeprazole to be more effective than placebo in relieving heartburn and various other gastrointestinal symptoms. Data among patients with Barrett's oesophagus suggest rabeprazole 20 mg/day may be more effective than placebo in maintaining healing of associated oesophagitis after 1 year of treatment. One-week triple *Helicobacter pylori* eradication therapy with rabeprazole plus clarithromycin and amoxicillin achieved eradication rates of > or =85%. Rabeprazole is as effective as omeprazole and lansoprazole when included as part of a triple-therapy regimen for the eradication of *H. pylori*. Eradication rates of >90% were achieved when rabeprazole 20 to 40 mg/day was included as part of a

quadruple eradication regimen. As monotherapy for peptic ulcer healing and symptom relief, 4- to 8-week studies have shown rabeprazole 10 to 40 mg/day to be superior to placebo and ranitidine and have similar efficacy to omeprazole. Preliminary 1-year data among 16 patients with Zollinger-Ellison syndrome suggest rabeprazole 60 to 120 mg/day can resolve and prevent the recurrence of symptoms and endoscopic lesions associated with this condition. In clinical trials of up to 2 years' duration the tolerability of rabeprazole is similar to that of placebo, ranitidine and omeprazole. Common adverse events assigned to rabeprazole have been diarrhoea, headache, rhinitis, nausea, pharyngitis and abdominal pain. Histological changes and increases in serum gastrin levels were unremarkable and typical of proton pump inhibitors. No dosage adjustment is necessary in renal and mild to moderate hepatic impairment. **CONCLUSION:** Rabeprazole is a well tolerated proton pump inhibitor. It has proven efficacy in healing, symptom relief and prevention of relapse of peptic ulcers and GORD and can form part of effective *H. pylori* eradication regimens. It is an important alternative to H<sub>2</sub> antagonists and an additional treatment option to other proton pump inhibitors in the management of acid-related disorders.

Publication Types:

- Review
- Review, Tutorial

PMID: 11772142 [PubMed - indexed for MEDLINE]

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☐ 3: Drugs 2001;61(12):1801-33

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**Lansoprazole: an update of its place in the management of acid-related disorders.**

**Matheson AJ, Jarvis B.**

Adis International Limited, Mairangi Bay, Auckland, New Zealand. [demail@adis.co.nz](mailto:demail@adis.co.nz)

Lansoprazole is an inhibitor of gastric acid secretion and also exhibits antibacterial activity against *Helicobacter pylori* in vitro. Current therapy for peptic ulcer disease focuses on the eradication of *H. pylori* infection with maintenance therapy indicated in those patients who are not cured of *H. pylori* and those with ulcers resistant to healing. Lansoprazole 30 mg combined with amoxicillin 1g, clarithromycin 250 or 500mg, or metronidazole 400 mg twice daily was associated with eradication rates ranging from 71 to 94%, and ulcer healing rates were generally >80% in well designed studies. In addition, it was as effective as omeprazole- or rabeprazole-based regimens which included these antimicrobial agents. Maintenance therapy with lansoprazole 30 mg/day was significantly more effective than either placebo or ranitidine in preventing ulcer relapse. Importantly, preliminary data suggest that lansoprazole-based eradication therapy is effective in children and the elderly. In the short-term treatment of patients with gastro-oesophageal reflux disease (GORD), lansoprazole 15, 30 or 60 mg/day was significantly more effective than placebo, ranitidine 300 mg/day or cisapride 40 mg/day and similar in efficacy to pantoprazole 40 mg/day in terms of healing of oesophagitis. Lansoprazole 30 mg/day, omeprazole 20 mg/day and pantoprazole 40 mg/day all provided similar symptom relief in these patients. In patients with healed oesophagitis, 12-month maintenance therapy with lansoprazole 15 or 30 mg/day prevented recurrence and was similar to or more effective than omeprazole 10 or 20 mg/day. Available data in patients with NSAID-related disorders or acid-related dyspepsia suggest that lansoprazole is effective in these patients in terms of the prevention of NSAID-related gastrointestinal complications, ulcer healing and symptom relief. Meta-analytic data and postmarketing surveillance in >30,000 patients indicate that lansoprazole is well tolerated both as monotherapy and in combination with antimicrobial agents. After lansoprazole monotherapy commonly reported adverse events included dose-dependent diarrhoea, nausea/vomiting, headache and abdominal pain. After short-term treatment in patients with peptic ulcer, GORD, dyspepsia and gastritis the incidence of adverse events associated with lansoprazole was generally < or = 5%. Similar adverse events were seen in long-term trials, although the incidence was generally higher (< or = 10%). When lansoprazole was administered in combination with amoxicillin, clarithromycin or metronidazole adverse events included diarrhoea, headache and taste disturbance. In conclusion, lansoprazole-based triple therapy is an effective treatment option for the eradication of *H. pylori* infection in patients with peptic ulcer disease. Preliminary data suggest it may have an important role in the management of this infection in children and the elderly. In the short-term management of GORD, lansoprazole monotherapy offers a more effective alternative to histamine H<sub>2</sub>-receptor antagonists and initial data indicate that it is an effective short-term treatment option in children and adolescents. In adults lansoprazole maintenance therapy is also an established treatment option for the long-term management of this chronic disease. Lansoprazole has a role in the treatment and prevention of NSAID-related ulcers and the treatment of acid-related dyspepsia; however, further studies are needed to confirm its place in these indications. Lansoprazole has emerged as a useful and well tolerated treatment option in the management of acid-related disorders.

Publication Types:  
◦ Review  
◦ Review, Tutorial

PMID: 11693467 [PubMed - indexed for MEDLINE]

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☐ 4: Clin Pharmacokinet 2000 Oct;39(4):295-309

[Related Articles](#), [NEW Books](#), [LinkOut](#)

**Selection of drugs to treat gastro-oesophageal reflux disease: the role of drug interactions.**

Flockhart DA, Desta Z, Mahal SK.

Division of Clinical Pharmacology, Department of Medicine, Georgetown University Medical Center, Washington, DC 20007, USA. [flockhad@gusun.georgetown.edu](mailto:flockhad@gusun.georgetown.edu)

Gastro-oesophageal reflux disease is probably the most common acid-peptic disease in Western countries, and the successful treatment of mild to moderate disease with pharmacotherapy has become commonplace. A large number of effective drugs are now available, and so the decision-making process for physicians increasingly relies on considerations other than pure efficacy. Cost, adverse effects and drug interactions have therefore become important, particularly in the most vulnerable patients - children, the elderly and patients who are ill and are taking medications that may influence the efficacy of antireflux therapy. Important drug interactions with antacids include the prevention of the absorption of antibacterials such as tetracycline, azithromycin and quinolones. H2 antagonists, proton pump inhibitors and prokinetic agents undergo metabolism by the cytochrome P450 (CYP) system present in the liver and gastrointestinal tract. Cimetidine is an inhibitor of CYP3A and it may cause significant interactions with drugs of narrow therapeutic range and low bioavailability that are metabolised by these enzymes. The gastroparietal proton pump inhibitors lansoprazole, omeprazole and pantoprazole are all primarily metabolised by a genetically polymorphic enzyme, CYP2C19, that is absent from approximately 3% of Caucasians and 20% of Asians. These drugs may also interact with CYP3A, but to a lesser extent. Interactions with prokinetic agents carry the greatest potential for harm. Metoclopramide is a dopamine antagonist that may cause extrapyramidal effects when administered alone at high concentrations, or when coadministered with antipsychotic agents such as haloperidol or phenothiazines. Cisapride is clearly able to prolong the electrocardiographic QT interval and cause lethal ventricular arrhythmias when its metabolism is slowed by interaction with inhibitors of CYP3A, such as erythromycin, ketoconazole or itraconazole.

Publication Types:  
◦ Review  
◦ Review, Tutorial

PMID: 11069215 [PubMed - indexed for MEDLINE]

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☐ 5: Expert Opin Investig Drugs 2000 Jul;9(7):1537-44

[Related Articles](#), [NEW Books](#), [LinkOut](#)

**Novel therapeutic approaches to gastric and duodenal ulcers: an update.**

Dajani EZ, Klamut MJ.

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Over the last 25 years, a remarkable revolution in the pathophysiology and treatment of gastric and duodenal ulcers has occurred. Effective therapies were developed not only to heal ulcers, but also to cure most patients. The two principal causes for gastric and duodenal ulcers are either infection with *Helicobacter pylori* or the use of non-steroidal anti-inflammatory drugs (NSAIDs). With *H. pylori* eradication, gastric and duodenal ulcers are rapidly becoming historical diseases. This communication reviews the salient pharmacology of the novel anti-ulcer drugs currently in development, with particular emphasis on the treatment of gastric and duodenal ulcers. Intense research is currently focused on the development of proton pump inhibitors primarily for the treatment and prevention of gastroesophageal reflux disease. The older proton pump inhibitors, omeprazole and lansoprazole, are effective in healing gastric and duodenal ulcers. Furthermore, both drugs are effective in eradicating *H. pylori* when given with various antibiotics. Pantoprazole, rabeprazole and esomeprazole are new proton pump inhibitors,

which appear to have comparable therapeutic profiles with omeprazole and lansoprazole. Rebamipide is a new mucosal protective drug, which is effective in healing gastric ulcers. Polaprezinc and nocolprost are also mucosal protective drugs, which are in clinical development. However, none of these three cytoprotective drugs have been evaluated for their efficacy in eradicating *H. pylori* when given in combination with antibiotics. Likewise, no published literature exists on the use of these drugs for preventing NSAID-induced ulcers. With the rapid eradication of *H. pylori* currently happening in the developed world, the therapeutic challenge is now directed toward preventing NSAID-associated ulcer. Significant reduction of NSAID-induced ulcers is achieved by using continuous prophylactic anti-ulcer therapy (misoprostol or omeprazole) or by using NSAIDs possessing selective COX-2 inhibitory activity. However, outcome clinical studies are needed to compare the adjuvant anti-ulcer therapies given with COX-1 inhibitors versus the selective COX-2 inhibitors given alone.

Publication Types:

- Review
- Review, Tutorial

PMID: 11060758 [PubMed - indexed for MEDLINE]

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☐ 6: Drugs 2000 Aug;60(2):321-9; discussion 330-1

[Related Articles](#), [NEW Books](#), [LinkOut](#)

**Esomeprazole.**

**Spencer CM, Faulds D.**

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Esomeprazole, a new proton pump inhibitor, is the S-isomer of omeprazole and is the first such inhibitor to be developed as a single isomer. Esomeprazole provided better control of intragastric pH than omeprazole, lansoprazole and pantoprazole in trials conducted in patients with gastro-oesophageal reflux disease (GORD) or healthy volunteers ( $n = 20$  to  $115$ ). In 2 large randomised, double-blind multicentre trials esomeprazole 20 and/or 40mg for 8 weeks produced higher healing rates of erosive oesophagitis and better symptom control than omeprazole 20 mg in patients with GORD. Esomeprazole 10, 20 or 40mg once daily for 6 months maintained healing versus placebo ( $p < 0.001$ ) in patients with endoscopically confirmed healed erosive oesophagitis in 2 large randomised, double-blind multicentre trials. Similarly, symptom-driven on-demand use of esomeprazole effectively controlled symptoms of GORD (heartburn) for 6 months in 2 large placebo-controlled trials. Esomeprazole-based triple therapy for 7 days was as effective for eradication of *Helicobacter pylori* as longer omeprazole-based therapy in 2 randomised double-blind trials including about 450 patients each. Endoscopically confirmed ulcer healing 4 weeks after treatment initiation was reported in about 90% of patients with active duodenal ulcer in both treatment groups. Esomeprazole-based triple therapy for 10 days was more effective than esomeprazole plus clarithromycin for eradication of *H. pylori* in 233 patients.

Publication Types:

- Review
- Review, Tutorial

PMID: 10983736 [PubMed - indexed for MEDLINE]

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☐ 7: Am J Manag Care 2000 May;6(9 Suppl):S467-75

[Related Articles](#), [NEW Books](#), [LinkOut](#)

**New therapeutic options in the treatment of GERD and other acid-peptic disorders. Based on a presentation by Duane D. Webb, MD, FACG.**

Gastroesophageal reflux disease (GERD), or the regurgitation of gastric content into the esophagus, is an acid-peptic disorder that has a significant impact on both health and the quality of life. Because gastric acid plays a major role in the pathophysiology of this disease, acid neutralization/suppression has emerged as the cornerstone of GERD therapy. Currently, there are 3 classes of drugs used to increase gastric pH: antacids, histamine<sub>2</sub> receptor antagonists (H<sub>2</sub>RAs), and proton pump inhibitors (PPIs). Antacids act by neutralizing the pH of the stomach. However, because of their limited efficacy and short duration of action, they have not been shown to be effective in either the prevention or healing of GERD-induced esophageal injury. Moreover, numerous doses per day are often required to control GERD symptoms. A second class of agents, H<sub>2</sub>RAs, act by inhibiting a histamine-dependent biochemical pathway that stimulates acid secretion by the gastric parietal cell. However, because there are several other stimulatory pathways that also

contribute to acid secretion, a lack of consistent efficacy of H2RAs exists among individuals. Moreover, because there are several pathways leading to acid secretion, patients who receive H2RAs often experience tachyphylactic reactions to these drugs. The PPIs are the latest and most effective medications for the treatment of GERD. Unlike H2RAs, PPIs block acid secretion at its source--the proton pump of the gastric parietal cell. Studies have consistently shown that PPIs are more effective than H2RAs in resolving GERD symptoms, healing erosive esophagitis, and preventing esophageal injuries. PPIs are also effective in the treatment of acid-peptic disorders other than GERD, such as duodenal and gastric ulcers. Four PPIs are currently available in the United States: omeprazole, lansoprazole, rabeprazole, and pantoprazole.

Publication Types:

- Review
- Review, Tutorial

PMID: 10977486 [PubMed - indexed for MEDLINE]

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☐ 8: Clin Pharmacol Ther 2000 Jun;67(6):684-9

Related Articles, **NEW** Books, LinkOut

**Cure of refractory duodenal ulcer and infection caused by *Helicobacter pylori* by high doses of omeprazole and amoxicillin in a homozygous CYP2C19 extensive metabolizer patient.**

Furuta T, Takashima M, Shirai N, Xiao F, Hanai H, Ohashi K, Ishizaki T.

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furuta@akiha.hama-med.ac.jp

A 53-year old female patient with duodenal ulcer and *Helicobacter pylori* infection was treated three times with a proton pump inhibitor-based triple therapy, such as lansoprazole-clarithromycin-amoxicillin (INN, amoxicilline) and lansoprazole-minocycline-cefacol. However, the *H pylori* infection was not cured. A culture test revealed that her infection was a clarithromycin-resistant but amoxicillin-sensitive strain of *H pylori*. Moreover, a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis revealed that she was a homozygous extensive metabolizer of cytochrome P450 (CYP) 2C19 (wt/wt). The usual dose of the proton pump inhibitor was therefore assumed to be insufficient for her and then she was treated with a high dose of omeprazole (120 mg/day) and amoxicillin (2,250 mg/day) for 2 weeks. The *H pylori* infection and the ulcer lesion were then cured. One of the factors associated with success or failure of cure of *H pylori* infection by the proton pump inhibitor-based triple therapy appeared to be CYP2C19 genotype status. Dual treatment with a sufficient dose of a proton pump inhibitor plus amoxicillin could cure *H pylori* infection even after the failure to cure *H pylori* infection by a usual proton pump inhibitor-based triple therapy in patients with the wt/wt homozygous extensive metabolizer genotype of CYP2C19.

Publication Types:

- Review
- Review of Reported Cases

PMID: 10872651 [PubMed - indexed for MEDLINE]

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☐ 9: Recent Prog Med 2000 Apr;91(4):191-210

Related Articles, **NEW** Books, LinkOut

**[Lansoprazole: an analysis of the clinical trials in the 3 years of 1997-1999]**

[Article in Italian]

Dobrilla G, Capurso L.

Ospedale Regionale, Bolzano.

Aim of this overview was to evaluate the main clinical trials with lansoprazole published from 1997 to 1999 in English-language journals, regarding gastroesophageal reflux disease, peptic ulcer, NSAID-induced ulcer, and ZES. Results of clinical trials for therapy and prevention of lesions/symptoms have been evaluated separately. In direct comparisons, lansoprazole alone (not combined with antibiotics) proves to be equieffective to other PPI and more effective than H2-RA in both therapy and prevention of GERD, peptic ulcer (a part from anti-Hp regimens) and NSAID-induced ulcer. Among Hp-eradicating regimens in patients with peptic ulcer or functional dyspepsia, lansoprazole-based triple therapy is equal

in efficacy to other PPI-based or RBC-based triple therapies and, in any case, significantly better than dual therapies. The in vitro anti-Hp activity of lansoprazole, more marked than with other PPI, does not seem to effort clinical advantages. Safety of lansoprazole is largely satisfactory and no different from other PPI and H2-RA.

Publication Types:

- Review
- Review, Tutorial

PMID: 10804753 [PubMed - indexed for MEDLINE]

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☐ 10: Yale J Biol Med 1999 Mar-Jun;72(2-3):169-72

[Related Articles](#), [NEW Books](#), [LinkOut](#)

### **Drugs, bugs, and esophageal pH profiles.**

**Robinson M.**

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Until relatively recently, gastroesophageal reflux disease (GERD) was thought to be a relatively trivial problem, and pharmaceutical companies initially had remarkably little interest in clinical trials for GERD. Over the last ten years, GERD therapy has become the subject of intense interest, since reflux disease is now recognized as a major market for antisecretory and prokinetic drugs. Even low-technology antacids are now known to effectively neutralize esophageal acid prevent acid reflux for up to 90 minutes. Esophageal pH profiling is known to be an excellent surrogate for clinical efficacy of GERD drugs, particularly in erosive esophagitis. Years ago, famotidine normalized esophageal mucosal exposure to pH < 4.0 only when administered in doses of 40 mg twice a day. Subsequent studies confirmed that multiple daily dosing of histamine-2 receptor antagonists (H2RAs) was mandatory for GERD treatment, with clear dose-response relationships for each agent. Proton pump inhibitors (PPIs) have each been carefully assessed in terms esophageal and gastric pH profiles. Omeprazole has a particularly flat dose response curve, making it difficult to differentiate pH or clinical effects of 20 vs. 40 mg doses. Improved rapidity of onset and/or enhanced potency is demonstrable in pH data obtained with lansoprazole, rabeprazole and pantoprazole. Such differences will translate to improved clinical efficacy, based on the meta-analyses of Richard Hunt and his group in Canada that correlate pH effects and symptom relief/healing. PPI's have dependably surpassed H2RAs and prokinetic drugs in management of the more severe grades of esophagitis. Helicobacter pylori has a peculiar relationship to GERD. There has been some concern that PPIs given to patients with H. pylori might accelerate development of severe atrophic gastritis. It is also now known that eradication of H. pylori may increase symptomatic GERD (possibly as a result of increased gastric acid secretion once the bacteria have been eliminated). New data confirm nocturnal breakthrough of acid secretion and esophageal acid exposure in three-fourths of patients on omeprazole 20 mg twice daily. This nocturnal acidity can be controlled more effectively with a nighttime dose of an H2RA than with a third dose of omeprazole. Control of acid secretion and improved gastric and esophageal pH profiles are goals of modern GERD therapy, and the product that most cost effectively normalizes esophageal acid exposure will have a substantial advantage in the ever-growing GERD marketplace.

Publication Types:

- Review
- Review, Tutorial

PMID: 10780578 [PubMed - indexed for MEDLINE]

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☐ 11: Am J Gastroenterol 1999 Nov;94(11 Suppl):S17-24

[Related Articles](#), [NEW Books](#), [LinkOut](#)

### **Treatment advances in acid secretory disorders: the promise of rapid symptom relief with disease resolution.**

**Earnest DL, Robinson M.**

The University of Arizona Health Sciences Center, Tucson 85724, USA.

Gastric acid-related disorders are common clinical problems associated with a wide range of symptoms. Important advances have occurred over the last 20 yr that have improved our understanding of these disorders as well as our approach to treatment. Today, control of

gastric acid secretion represents the cornerstone of effective management of both peptic ulcer disease and gastroesophageal reflux disease (GERD). A variety of acid-reducing strategies are now available to clinicians to manage symptoms and control or resolve disease. Antacids offer rapid symptomatic relief but probably have little effect on overall disease progression. Histamine-2 receptor antagonists can also provide good initial symptomatic treatment in peptic ulcer disease and in mild to moderate GERD. However, problems with postmeal acid control and tachyphylaxis may detract from their long-term usefulness. The availability of proton pump inhibitors (PPIs), which block the final process in H<sup>+</sup> ion secretion, has revolutionized our approach to the management of patients with acid secretory disorders. The currently available PPIs, omeprazole and lansoprazole, enable us to control symptoms effectively and safely, hasten healing, and minimize disease recurrence. New PPIs, such as rabeprazole and pantoprazole, will further expand our treatment options and may offer even greater possibilities with regard to rapid symptomatic relief and disease resolution.

Publication Types:

- Review
- Review, Tutorial

PMID: 10565605 [PubMed - indexed for MEDLINE]

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☐ 12: Aliment Pharmacol Ther 1999 Oct;13 Suppl 5:11-6

Related Articles, [NEW](#) Books, LinkOut

**Review article: pharmacokinetic concerns in the selection of anti-ulcer therapy.**

Lew EA.

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Rabeprazole is a new, highly potent proton pump inhibitor (PPI) being introduced for the treatment of disorders of gastric acid hypersecretion. Rabeprazole joins other drugs in this class, such as omeprazole, pantoprazole, and lansoprazole, which share a common mechanism of action. Each of these drugs is a substituted benzimidazole, which inhibits activity of the H<sup>+</sup>, K<sup>+</sup>-ATPase located on the apical surface of parietal cells, thereby preventing the secretion of gastric acid. As a result of structural and functional similarities, the PPIs share many pharmacokinetic features. They have comparable rates of absorption, maximum plasma concentrations, and total drug absorptions resulting in similar bioavailability after single-dose administration. With multiple dosing, rabeprazole differs from omeprazole in that its pharmacokinetic profile does not change significantly over the course of therapy. All the PPIs are metabolized rapidly, resulting in short half-lives. However, their duration of activity is much longer, due to the way in which they bind to H<sup>+</sup>, K<sup>+</sup>-ATPase. All are metabolized by hepatic cytochrome P450 enzymes, although only omeprazole has demonstrated significant interactions with other drugs metabolized by this pathway. Rabeprazole, which has a low potential for interacting with drugs metabolized by cytochrome P450, does not interfere with the absorption of digoxin and ketoconazole because of its antisecretory effects. The pharmacokinetics of rabeprazole are altered slightly in elderly subjects and in patients with renal and moderate hepatic disease. However, the pharmacokinetic findings suggest that no dosage adjustment is required in these special populations.

Publication Types:

- Review
- Review, Tutorial

PMID: 10555604 [PubMed - indexed for MEDLINE]

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☐ 13: Drugs 1999 Oct;58(4):725-42

Related Articles, [NEW](#) Books, LinkOut

**Rabeprazole: a review of its use in acid-related gastrointestinal disorders.**

Langtry HD, Markham A.

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Rabeprazole is an inhibitor of the gastric proton pump. It causes dose-dependent inhibition of acid secretion and has a more rapid onset of action than omeprazole. Duodenal ulcers healed faster after treatment with rabeprazole 20 or 40 mg/day than placebo or ranitidine



150 mg 4 times daily and at a generally similar rate to omeprazole 20 mg/day in patients with duodenal ulcers; rabeprazole was similar or superior to these agents in relieving symptoms. Rabeprazole 20 and 40 mg/day healed gastric ulcers faster than placebo, and rabeprazole 20 mg/day healed ulcers at a similar healing rate, to omeprazole 20 mg/day in well controlled 6-week studies. Gastric ulcer symptom relief with rabeprazole was similar or superior to that provided by omeprazole or placebo. In 8-week studies in patients with gastro-oesophageal reflux disease (GERD), rabeprazole 10, 20 and 40 mg/day were more effective than placebo, rabeprazole 20 mg/day was more effective than ranitidine 150 mg twice daily, and rabeprazole 20 mg/day was similar in efficacy to omeprazole 20 mg/day. Symptom relief with rabeprazole in 8-week trials in patients with GERD was superior to that provided by placebo, and similar to ranitidine or omeprazole. Rabeprazole was similar to omeprazole and superior to placebo in both maintenance of healing and prevention of symptoms in patients with healed GERD in 1-year studies. One-week triple therapy with rabeprazole 20 mg twice daily plus 2 antibacterial agents achieved > or = 90% *Helicobacter pylori* eradication, but, as would be expected, a regimen of rabeprazole 20 mg twice daily plus 1 antibacterial agent was less successful. The drug was as effective as omeprazole and lansoprazole as part of triple therapy for *H. pylori* eradication. Rabeprazole successfully reduced acid output to target levels and prevented further pathological changes in 10 patients with Zollinger-Ellison syndrome. Usual dosages of rabeprazole are 20 mg/day for 4 weeks to treat duodenal ulcers, 6 weeks for gastric ulcers and 8 weeks for GERD, although some patients with duodenal ulcer may respond to a 10 mg/day dosage. For long term maintenance of GERD healing, 10 or 20 mg daily doses are adequate. Patients with hypersecretory states may need individualised dosages starting at 60 mg/day. The drug was well tolerated in clinical trials, with headache, rash, infection, diarrhoea and flu syndrome as the most common adverse events. In conclusion, rabeprazole appears to be a well tolerated proton pump inhibitor with a rapid onset of action and a low potential for drug interactions. The drug may be used to achieve healing and the relief of symptoms of duodenal ulcer, gastric ulcer and GERD, maintain GERD healing, and can form part of effective regimens to eradicate *H. pylori*.

Publication Types:

- Review
- Review, Tutorial

PMID: 10551440 [PubMed - indexed for MEDLINE]

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☐ 14: Scand J Gastroenterol Suppl 1999;230:3-8

Related Articles, **NEW** Books, LinkOut

**Onset of action of antisecretory drugs: beneficial effects of a rapid increase in intragastric pH in acid reflux disease.**

Pipkin GA, Mills JG.

Dept. of Gastroenterology, Glaxo Wellcome Research and Development, Uxbridge, UK.

**BACKGROUND:** The majority of patients who have symptomatic acid reflux disease will have a normal oesophageal mucosa or will have only a mild degree of oesophagitis. Treatment to relieve symptoms as they occur may be the best way to manage these patients, to whom the speed of symptom relief is of primary importance. The effervescent complex used to formulate effervescent ranitidine contains sodium bicarbonate and monosodium citrate, and has, therefore, an intrinsic acid-neutralizing capacity in addition to the well-documented antisecretory activity. **METHODS:** The results of studies of the effects of effervescent ranitidine tablets on intragastric pH and on the relief of heartburn are reviewed. **RESULTS AND CONCLUSIONS:** When compared with the standard ranitidine tablet, the effervescent formulation results in a significantly greater and more rapid rise in intragastric pH in the hour immediately after dosing. Comparative studies show that intragastric pH is raised significantly faster after a single dose of effervescent ranitidine than after a famotidine rapid release tablet and after either an omeprazole or a lansoprazole capsule. In patients with acid reflux disease, effervescent ranitidine provides quicker relief of symptoms than a standard tablet and is preferred by most patients for this reason. The majority of patients (more than 80%) report symptom relief within 60 min of taking effervescent ranitidine.

Publication Types:

- Review
- Review, Tutorial

PMID: 10499455 [PubMed - indexed for MEDLINE]

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☐ 15: Can J Gastroenterol 1999 Apr;13(3):213-7

Related Articles, **NEW** Books, LinkOut

**Canadian Helicobacter pylori Consensus Conference update: infections in adults. Canadian Helicobacter Study Group.****Hunt RH, Fallone CA, Thomson AB.**

Division of Gastroenterology, Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

The first Canadian Helicobacter pylori Consensus Conference took place in April 1997. The initial recommendations of the conference were published in early 1998. An update meeting was held in June 1998, and the present paper updates and complements the earlier recommendations. Key changes included the following: the recommendation for testing and treating H pylori infection in patients with known peptic ulcer disease was extended to testing and treating patients with ulcer-like dyspepsia; it was decided that the urea breath test (not serology) should be used for routine diagnosis of H pylori infection unless endoscopy is indicated for another reason; and recommended therapies were a twice daily, seven-day regimen of a proton pump inhibitor (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg) or ranitidine bismuth citrate 400 mg, plus clarithromycin 500 mg and amoxicillin 1000 mg, or plus clarithromycin 500 or 250 mg and metronidazole 500 mg. The need was reiterated to have funding for readily accessible, accurate testing for H pylori infection with the urea breath test. It was strongly recommended that regional centres be established to monitor the prevalence of antibiotic-resistant H pylori infections. The initial consensus document referred to pediatric issues that were not addressed in this update but were the subject of a subsequent Canadian Helicobacter Study Group meeting, and will be published later in 1999.

**Publication Types:**

- Consensus Development Conference
- Guideline
- Practice Guideline
- Review

PMID: 10331931 [PubMed - indexed for MEDLINE]

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**16:** Postgrad Med J 1998 Nov;74(877):653-7Related Articles, **NEW** Books, LinkOut**Barrett's oesophagus.****Navaratnam RM, Winslet MC.**

University Department of Surgery, Royal Free Hospital, London, UK.

Barrett's oesophagus represents the replacement of stratified squamous epithelium by metaplastic columnar epithelium for 3 cm of the distal oesophagus. Gastro-oesophageal reflux, which affects 40% of the adult population, is the principal aetiological factor. This results in predominantly acid but also bile reflux (due to duodenogastrooesophageal reflux) through the lower oesophageal sphincter, transient relaxation of which accounts for the main mechanism of reflux. Conventional Barrett's oesophagus is reported in 11-13% of patients with symptomatic reflux and short segment Barrett's oesophagus (< 3.0 cm) in 18%. Approximately 50% of these patients have recognised complications on presentation, eg, carcinoma (15%). The disparity between clinical symptoms and endoscopic severity is due to reduced oesophageal mucosal sensitivity as a consequence of prolonged mucosal acid exposure. These rather alarming figures combined with the knowledge that Barrett's oesophagus is a pre-malignant condition (the diagnosis is associated with a 25-130-fold increase of malignancy) may account for the substantial increase in junctional gastrooesophageal malignancies. Symptomatic Barrett's oesophagus should be managed with full-dose proton pump inhibitors, eg, lansoprazole. Anti-reflux surgery should be reserved for the medically fit patient with recurrent symptomatic relapse in the histological absence of premalignant change. There is no evidence suggesting that surgery can be used as a prophylactic measure against malignancy. Encouraging short-term results have been obtained with photodynamic therapy in the management of high-grade dysplasia. However, columnar epithelium has been found underlying the regenerated squamous epithelium, suggesting that life-long surveillance is warranted.

**Publication Types:**

- Review
- Review, Tutorial

PMID: 10197195 [PubMed - indexed for MEDLINE]

☐ 17: Drug Saf 1999 Feb;20(2):195-205Related Articles, [NEW Books](#), [LinkOut](#)**Safety profile of Lansoprazole: the US clinical trial experience.**

Freston JW, Rose PA, Heller CA, Haber M, Jennings D.

Department of Medicine, University of Connecticut Health Center, Farmington 06032, USA.  
freston@nso.uchc.edu

**OBJECTIVE:** Lansoprazole has undergone extensive clinical evaluation for the treatment of acid-peptic diseases. The aim of this study was to define the safety profile of lansoprazole and compare it to that of other therapeutic agents evaluated in the same controlled trials. **METHODS:** The clinical safety profile of lansoprazole and comparative agents (placebo, ranitidine and omeprazole) was reviewed for 3281 patients who participated in short term (up to 8 weeks) and long term (up to 56 months) clinical trials conducted in the US. Adverse events, laboratory value changes and gastric biopsy changes that occurred during treatment were compared statistically for differences between treatments. **RESULTS:** The incidence of adverse events and number of patients discontinuing treatment because of adverse events was similar for lansoprazole and comparative agents. Other than elevated serum gastrin levels, a known effect of proton pump inhibitors, no trends in laboratory changes were observed. Median values for gastrin levels remained within the normal range; about 2% of patients had gastrin levels >400 pg/ml at any time, while <1% had 2 or more gastrin values >500 pg/ml. Values returned to baseline levels after therapy was discontinued. No significant changes in gastric endocrine cell growth from baseline to final visit were observed, nor was there evidence of dysplasia or neoplasia. **CONCLUSION:** Lansoprazole is well tolerated for both short and long term treatment of acid-related disease. The tolerability of lansoprazole is comparable to that of ranitidine, omeprazole and placebo in the treatment of these diseases.

## Publication Types:

- Review
- Review, Tutorial

PMID: 10082075 [PubMed - indexed for MEDLINE]

☐ 18: Nippon Rinsho 1999 Jan;57(1):127-33Related Articles, [NEW Books](#), [LinkOut](#)**[Eradication rate and side effect from a point of view of Helicobacter pylori eradication of peptic ulcer disease in dual therapy or new triple therapy]**

[Article in Japanese]

Iwasaki A.

3rd Department of Internal Medicine, Surugadai Nihon University Hospital.

Eradication rate of Helicobacter pylori in dual therapy (omeprazole/amoxicillin) are reported in the range of 28-91%, side effect such as loose stool and skin reaction are reported 3.9-16.8%. In our study, eradication rate in dual therapy is 69.6% (lansoprazole/amoxicillin) and 74.0% (lansoprazole/clarithromycin). In triple therapy, eradication rate is 93.8% (lansoprazole/amoxicillin/clarithromycin), 94.4% (lansoprazole/amoxicillin/metronidazole) and 100.0% (lansoprazole/clarithromycin/metronidazole). There is no difference eradication rate between 1 week (89.2%) and 2 weeks (92.9%) regimen. In general, eradication rate of new triple therapy is effective in the range of 80-100%, and side effect are reported in 1.7-49%. However, Suzuki et al reported side effect decreased in new triple therapy adding mucosal protective agent.

## Publication Types:

- Review
- Review, Tutorial

PMID: 10036949 [PubMed - indexed for MEDLINE]

☐ 19: Drug Saf 1998 Oct;19(4):325-37Related Articles, [NEW Books](#), [LinkOut](#)**Treating gastro-oesophageal reflux disease during pregnancy and lactation: what are the safest therapy options?**

**Broussard CN, Richter JE.**

Department of Gastroenterology, The Cleveland Clinic Foundation, Ohio 44195, USA.

Gastro-oesophageal reflux and heartburn are reported by 45 to 85% of women during pregnancy. Typically, the heartburn of pregnancy is new onset and is precipitated by the hormonal effects of estrogen and progesterone on lower oesophageal sphincter function. In mild cases, the patient should be reassured that reflux is commonly encountered during a normal pregnancy: lifestyle and dietary modifications may be all that are required. In a pregnant woman with moderate to severe reflux symptoms, the physician must discuss with the patient the benefits versus the risks of using drug therapy. Medications used for treating gastro-oesophageal reflux are not routinely or vigorously tested in randomised, controlled trials in women who are pregnant because of ethical and medico-legal concerns. Safety data are based on animal studies, human case reports and cohort studies as offered by physicians, pharmaceutical companies and regulatory authorities. If drug therapy is required, first-line therapy should consist of nonsystemically absorbed medications, including antacids or sucralfate, which offer little, if any, risk to the fetus. Systemic therapy with histamine H2 receptor antagonists (avoiding nizatidine) or prokinetic drugs (metoclopramide, cisapride) should be reserved for patients with more severe symptoms. Proton pump inhibitors are not recommended during pregnancy except for severe intractable cases of gastrooesophageal reflux or possibly prior to anaesthesia during labour and delivery. In these rare situations, animal teratogenicity studies suggests that lansoprazole may be the best choice. Use of the least possible amount of systemic drug needed to ameliorate the patient's symptoms is clearly the best for therapy. If reflux symptoms are intractable or atypical, endoscopy can safely be performed with conscious sedation and careful monitoring the mother and fetus.

Publication Types:

- Review
- Review, Tutorial

PMID: 9804446 [PubMed - indexed for MEDLINE]

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☐ 20: Drugs 1998 Sep;56(3):447-86

[Related Articles](#), [NEW Books](#), [LinkOut](#)

**Omeprazole. A review of its use in *Helicobacter pylori* infection, gastro-oesophageal reflux disease and peptic ulcers induced by nonsteroidal anti-inflammatory drugs.**

**Langtry HD, Wilde MI.**

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Omeprazole is a well studied proton pump inhibitor that reduces gastric acid secretion. This review examines its use in *Helicobacter pylori* infection, gastro-oesophageal reflux disease (GORD) with or without oesophagitis and gastrointestinal damage caused by nonsteroidal anti-inflammatory drugs (NSAIDs). Optimal omeprazole regimens for anti-*H. pylori* therapy are those that administer the drug at a dosage of 40 mg/day (in 1 or 2 divided doses) for 7, 10 or 14 days in combination with 2 antibacterial agents. As a component of 3-drug regimens in direct comparative studies, omeprazole was at least as effective as lansoprazole, pantoprazole, bismuth compounds and ranitidine. However, a meta-analysis suggests that triple therapies with omeprazole are more effective than comparable regimens containing ranitidine, lansoprazole or bismuth. Omeprazole also appears to be successful in triple therapy regimens used in children with *H. pylori* infection. In patients with acute GORD with oesophagitis, omeprazole is at least as effective as lansoprazole or pantoprazole in promoting healing, and superior to ranitidine, cimetidine or cisapride in oesophagitis healing and symptom relief. Omeprazole was similar to lansoprazole and superior to ranitidine in preventing oesophagitis relapse in patients with all grades of oesophagitis, but may be superior to lansoprazole or pantoprazole in patients with more severe disease. More patients with symptomatic GORD without oesophagitis experienced symptom relief after short term treatment with omeprazole than with ranitidine, cisapride or placebo, and symptoms were more readily prevented by omeprazole than by cimetidine or placebo. Omeprazole was effective in healing and relieving symptoms of reflux oesophagitis in children with oesophagitis refractory to histamine H2 receptor antagonists. Omeprazole is superior to placebo in preventing NSAID-induced gastrointestinal damage in patients who must continue to take NSAIDs. It is also similar to misoprostol and superior to ranitidine in its ability to heal NSAID-induced peptic ulcers and erosions, and superior to misoprostol, ranitidine or placebo in its ability to prevent relapse. In long and short term studies, omeprazole was well tolerated, with diarrhoea, headache, dizziness, flatulence, abdominal pain and constipation being the most commonly reported adverse events. Usual omeprazole dosages, alone or combined with other agents, are 10 to 40 mg/day for adults

and 10 to 20 mg/day for children. CONCLUSIONS: Omeprazole is a well studied and well tolerated agent effective in adults or children as a component in regimens aimed at eradicating *H. pylori* infections or as monotherapy in the treatment and prophylaxis of GORD with or without oesophagitis or NSAID-induced gastrointestinal damage.

Publication Types:

- Review
- Review, Academic

PMID: 9777317 [PubMed - indexed for MEDLINE]

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☐ 21: Pol Merkuriusz Lek 1998 Jun;4(24):339-41

Related Articles, **NEW** Books

**[Lansoprazol ++ : a new proton pump inhibitor]**

[Article in Polish]

Baczek J, Laskowicz G.

III Oddziału Chorob Wewnętrznych ZOZ w Cieszynie, ordynator.

Lansoprazole is the new proton pump inhibitor, decreasing the volume of gastric acid secretions and inhibiting secretion of gastric acid and pepsin. Lansoprazole appears to be more effective in therapy of gastric ulcer and duodenal ulcer in comparison with H<sub>2</sub>-receptor antagonists and omeprazole. Reflux oesophagitis and Zollinger-Ellison syndrome are also healed by Lansoprazole. The best results in the treatment of patients with peptic ulcer, reflux oesophagitis and Zollinger-Ellison syndrome were occurred after a daily 30 mg dose of Lansoprazole. Treatment of patients with duodenal ulcer should be continued for 2 to 4 week and the case of gastric ulcer as well as reflux oesophagitis should be prolonged till 4 to 8 week. Lansoprazole is well tolerated, reported adverse effects are similar to the incidence observed in patients treated with other proton pump inhibitors.

Publication Types:

- Review
- Review, Tutorial

PMID: 9771021 [PubMed - indexed for MEDLINE]

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☐ 22: Aliment Pharmacol Ther 1998 Sep;12(9):823-37

Related Articles, **NEW** Books, LinkOut

Comment in:

- Aliment Pharmacol Ther. 1999 Mar;13(3):437-9.



**Review article: one-week clarithromycin triple therapy regimens for eradication of *Helicobacter pylori*.**

Pipkin GA, Williamson R, Wood JR.

Department of Gastroenterology, Glaxo Wellcome Research and Development, Uxbridge, UK.

BACKGROUND: One-week triple therapies have been endorsed as the treatment regimens of choice for eradication of *Helicobacter pylori* infection. Those that include clarithromycin appear to be the most effective. AIM: To review reports of triple therapies that include clarithromycin. METHODS: Reports were identified from the literature to May 1998. The variation between study designs prevents a formal meta-analysis. A measure of the relative efficacies of regimens has, however, been gained by comparison and by pooling of intention-to-treat eradication rates. RESULTS: One hundred and ninety-two studies were identified which included 264 treatment arms of a 1-week triple therapy composed of clarithromycin with amoxycillin or a nitroimidazole (metronidazole or tinidazole), and either ranitidine bismuth citrate or a proton pump inhibitor (omeprazole, lansoprazole or pantoprazole). From reports of these studies, an intention-to-treat *H. pylori* eradication rate could be determined from 210 treatment arms of 151 studies. CONCLUSIONS: There is little to choose between the efficacies of 1-week clarithromycin-based triple therapy eradication regimens. However, those comprising clarithromycin, a nitroimidazole and either ranitidine bismuth citrate or a high dose of omeprazole are, in general, the most effective. Against antibiotic-resistant strains of *H. pylori*, regimens including ranitidine bismuth citrate may be more effective than those including a proton pump inhibitor.

## Publication Types:

- Review
- Review, Academic

PMID: 9768524 [PubMed - indexed for MEDLINE]

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☐ 23: Postgrad Med 1998 Jul;104(1):155-8, 163-4Related Articles, **NEW** Books, LinkOut**Zollinger-Ellison syndrome. Improved treatment options for this complex disorder.****Qureshi W, Rashid S.**

Baylor College of Medicine, USA. wqureshi@bcm.tmc.edu

Zollinger-Ellison syndrome is a rare disorder characterized by severe peptic ulcer disease, gastric acid hypersecretion, and non-beta islet cell tumors of the pancreas. Most gastrinomas are found within an anatomic area known as the gastrinoma triangle. However, they commonly occur in extrapancreatic sites in multiple endocrine neoplasia type 1 syndrome. In patients in whom Zollinger-Ellison syndrome is suspected, laboratory evidence of hypergastrinemia and hyperacidity establishes the diagnosis. Until the advent of proton pump inhibitors, total gastrectomy was the treatment of choice. Therapy with these agents (eg, omeprazole, lansoprazole) can prevent ulcer disease. However, surgical removal of gastrinomas offers a chance for cure and can improve longevity by preventing the malignant spread of the tumors.

## Publication Types:

- Review
- Review, Tutorial

PMID: 9676569 [PubMed - indexed for MEDLINE]

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☐ 24: Helicobacter 1997 Dec;2(4):159-71Related Articles, **NEW** Books**Clarithromycin dual therapy regimens for eradication of Helicobacter pylori: a review.****Pipkin GA, Dixon JS, Williamson R, Wood JR.**

Department of Gastroenterology, Glaxo Wellcome Research and Development, Uxbridge, UK.

**BACKGROUND.** Peptic ulcer disease can be cured by eradication of *Helicobacter pylori* during treatment to heal the ulcer. Dual therapy regimens were among the first to be granted approval for use. Reports of dual therapies including clarithromycin as the sole antibiotic are reviewed. **METHODS.** Reports were identified from literature up to May 1997. Information reviewed included patient population, medical diagnosis, trial design, eradication regimens, and *H. pylori* eradication rates. The great diversity between studies limits formal meta-analysis but a measure of relative efficacy has been obtained by comparison of eradication rates derived by clearly defined methods and by pooling data. **RESULTS.** Seventy-five reports of trials with 104 dual therapy treatment arms were reviewed. *H. pylori* eradication rates reported with ranitidine bismuth citrate plus clarithromycin range from 70-96% with a pooled observed rate of 85%. With omeprazole plus clarithromycin, reported eradication rates range from 27-90% with the pooled reported rate being 66%. Few data are available with either lansoprazole or ranitidine hydrochloride plus clarithromycin. **CONCLUSION.** High *H. pylori* eradication rates derived by consistent and clearly defined methods have been seen with ranitidine bismuth citrate plus clarithromycin. Lower and more variable rates are reported with clarithromycin and either a proton pump inhibitor or a histamine H2-receptor antagonist.

## Publication Types:

- Review
- Review, Tutorial

PMID: 9421117 [PubMed - indexed for MEDLINE]

☐ 25: Pharmacotherapy 1997 Sep-Oct;17(5):938-58Related Articles, **NEW** Books, LinkOut**Identification, diagnosis, and treatment of acid-related diseases in the elderly: implications for long-term care.****Garnett WR, Garabedian-Ruffalo SM.**

School of Pharmacy, Virginia Commonwealth University, Medical College of Virginia, Richmond 23298-0533, USA.

Acid-related disorders such as peptic ulcer disease and gastroesophageal reflux disease occur frequently in the elderly and are associated with a high frequency of morbidity and mortality. The proton pump inhibitors lansoprazole and omeprazole produce faster rates of healing and greater symptomatic relief in patients with acid-related disorders than histamine2-receptor antagonists, are well tolerated, and are associated with few adverse events. Compared with omeprazole, which interacts with diazepam, warfarin, and phenytoin, lansoprazole produces only a minor increase in theophylline clearance. Proton pump inhibitors in combination with antibiotic therapy can eradicate *Helicobacter pylori*, the main risk factor in the recurrence of peptic ulcer disease, obviating the need for maintenance therapy. Long-term acid suppression with proton pump inhibitors may be necessary to prevent the recurrence of gastroesophageal reflux disease. The safety and efficacy profile of these agents makes them ideal for the treatment of acid-related diseases in elderly patients.

## Publication Types:

- Review
- Review, Academic

PMID: 9324183 [PubMed - indexed for MEDLINE]

☐ 26: Am J Manag Care 1997 Oct;3(10):1528-34Related Articles, **NEW** Books, LinkOut**Evolving therapy for *Helicobacter pylori* infection: efficacy and economic impact in the treatment of patients with duodenal ulcer disease.****Cutler AF, Vakil N.**

Section of Gastroenterology, Sinai Hospital, Detroit, MI 48235, USA.

*Helicobacter pylori* infection is present in most patients with duodenal ulcer disease, and cure of *H pylori* infection has been shown to dramatically reduce ulcer recurrence. Therapeutic strategies for duodenal ulcer disease have rapidly evolved over the past several years in an effort to consistently cure *H pylori* infection in a safe, cost-efficient manner. This paper reviews the effectiveness of treatments for *H pylori* infection in patients assessed with duodenal ulcer disease. The impact of clinical success on economic effectiveness has been determined in a recent prospective outcomes trial. Treatments with clarithromycin plus omeprazole or clarithromycin plus ranitidine-bismuth-citrate (RBC) provide consistent cure of *H pylori* infection, with eradication rates of 70% to 80%. Recent studies suggest that higher rates of eradication are possible with triple combination therapy (e.g., clarithromycin plus a second antibiotic and a proton pump inhibitor or RBC), but the optimal triple therapy regimen (including the combination of drugs, dosage, and duration of treatment) has not yet been defined. A recent 1-year prospective outcomes trial has demonstrated that eradication therapy with clarithromycin and omeprazole, compared with standard antisecretory therapy, provides measurable savings in utilization of ulcer-related health-care resources. Combination therapy with clarithromycin plus omeprazole, clarithromycin plus RBC, or clarithromycin plus lansoprazole and amoxicillin have been approved for the treatment of *H pylori* infection in patients with duodenal ulcer disease. Economic analysis has confirmed that cure of *H pylori* infection not only contributes to the clinical resolution of duodenal ulcer disease, but also provides economic advantages by reducing costs associated with recurrence.

## Publication Types:

- Review
- Review, Tutorial

PMID: 10178459 [PubMed - indexed for MEDLINE]

☐ 27: Drugs 1997 Sep;54(3):473-500Related Articles, **NEW** Books, LinkOut

## **Lansoprazole. An update of its pharmacological properties and clinical efficacy in the management of acid-related disorders.**

Langtry HD, Wilde MI.

Adis International Limited, Auckland, New Zealand. demail@adis.co.nz

Lansoprazole is a proton pump inhibitor that reduces gastric acid secretion. It has proved effective in combination regimens for the eradication of *Helicobacter pylori* and as monotherapy to heal and relieve symptoms of gastric or duodenal ulcers and gastro-oesophageal reflux. After initial healing, it may be used to prevent recurrence of oesophageal erosions or peptic ulcers in patients in whom *H. pylori* is not the major cause of ulceration and to reduce basal acid output in patients with Zollinger-Ellison syndrome. Usual dosages are 15 to 60 mg/day, although dosages of  $\leq$  180 mg/day have been used in patients with hypersecretory states. In patients with duodenal or gastric ulcer, short term lansoprazole monotherapy was similar to omeprazole and superior to histamine H<sub>2</sub> receptor antagonists in achieving healing rates  $> 90\%$ . Lansoprazole was as effective a component of *H. pylori* eradication regimens as omeprazole, tripotassium dicitrato bismuthate (colloidal bismuth subcitrate) or ranitidine. Lansoprazole was superior to ranitidine in symptom relief and healing of gastro-oesophageal reflux disease and tended to relieve symptoms more rapidly than omeprazole, although initial healing was similar. As maintenance treatment, lansoprazole was similar to omeprazole and superior to ranitidine in relieving symptoms and preventing relapse. Lansoprazole was also superior to ranitidine in healing and relieving symptoms of oesophageal erosions associated with Barrett's oesophagus; healing was maintained for a mean of 2.9 years in  $\geq 70\%$  of patients. Lansoprazole was also superior to ranitidine in prophylaxis of redilatation of oesophageal strictures. After  $\geq 4$  years of use in patients with Zollinger-Ellison syndrome, lansoprazole 60 to 180 mg/day effectively controlled basal acid output. Dosages may be reduced in some patients once healing and symptom relief has been achieved. Preliminary studies of lansoprazole in patients at risk of aspiration pneumonia or stress ulcers show promise. Although studies show lansoprazole is potentially effective in treating gastrointestinal bleeding, future studies should assess patients' *H. pylori* status. Lansoprazole has been well tolerated in clinical trials, with headache, diarrhoea, dizziness and nausea appearing to be the most common adverse effects. Tolerability of lansoprazole does not deteriorate with age and the drug is well tolerated in long term use ( $\leq 4$  years) in patients with Zollinger-Ellison syndrome or reflux disease. Thus, lansoprazole is an important alternative to omeprazole and H<sub>2</sub> receptor antagonists in acid-related disorders. In addition to its efficacy in healing or maintenance treatment, it may provide more effective symptom relief than other comparator agents.

### Publication Types:

- Review
- Review, Academic

PMID: 9279507 [PubMed - indexed for MEDLINE]

☐ 28: Arzneimittelforschung 1997 Apr;47(4A):475-82

Related Articles, **NEW** Books, LinkOut

## **Anti-*Helicobacter pylori* activities of ebrotidine. A review of biochemical and animal experimental studies and data.**

Slomiany BL, Piotrowski J, Slomiany A.

Research Center, University of Medicine and Dentistry of New Jersey, Newark, USA.

Infection with *Helicobacter pylori* (*H. pylori*) is now recognized as a major factor in the pathogenesis of gastric disease, and the successful therapy regimens require a combination of H<sub>2</sub> blockers with gastroprotective and antimicrobial agents. Ebrotidine (N-[(E)-[2-[[[2-[(diaminomethylene) amino]-4-thiazolyl]methyl]thio]ethyl]amino]methylene]-4-bromo-benzenesulfonamide, CAS 100981-43-9, FI-3542) is the only drug combining acid-suppressant activity with remarkable gastroprotective and anti-*H. pylori* properties. The drug not only displays a potent anti-*H. pylori* activity alone, but also exerts a strong potentiating effect on the efficacy of antimicrobial agents commonly used for *H. pylori* eradication, and the successful ulcer therapy with ebrotidine induces a significant (4-fold) increase in the *H. pylori* aggregation titer of gastric mucin. Moreover, the drug exhibits a strong inhibitory effect on *H. pylori* urease activity, the extent of which exceeds that of ranitidine, omeprazole and lansoprazole. Ebrotidine has also been demonstrated to exert a potent inhibitory action on the enzymatic activities directed towards mucus perimeter of gastric mucosal defense, causing a marked inhibition of *H. pylori* protease, lipase and phospholipase A<sub>2</sub> activities. Another important property of ebrotidine is its ability to efficiently counteract the disruptive effects of *H. pylori*



lipopolysaccharide on the integrity of gastric epithelium. This includes countering the interference by the lipopolysaccharide in mucosal integrin receptor interaction with proteins of extracellular matrix and the reversal of *H. pylori* disruptive effect on the binding of mucin to its gastric epithelial receptor. Furthermore, most recent data indicate that ebrotidine has the ability to reverse the impairment caused by *H. pylori* in feedback inhibition of gastrin release by somatostatin. This activity of ebrotidine apparently stems from the drug's ability to counter the untoward effect of *H. pylori* on the binding of somatostatin to its specific receptor on the gastric mucosal G-cells. The unique combination of acid suppressant, gastroprotective and anti-*H. pylori* activities makes ebrotidine a drug of choice in the treatment of gastric disease caused by *H. pylori*.

Publication Types:

- Review
- Review, Academic

PMID: 9205747 [PubMed - indexed for MEDLINE]

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☐ 29: Am J Gastroenterol 1997 Apr;92(4 Suppl):44S-48S;  
discussion 49S-50S

[Related Articles](#), [NEW Books](#), [LinkOut](#)

### **Zollinger-Ellison syndrome: pathogenesis, diagnosis, and management.**

Hirschowitz BI.

Department of Medicine, University of Alabama School of Medicine, Birmingham 35294, USA.

Zollinger-Ellison syndrome (ZES) involves hypergastrinemia produced by gastrin-secreting tumor(s) of the pancreas or duodenum. Estimated to occur in 0.1-3 per million of the United States' population, the actual prevalence may be higher because ZES is often undetected with routine testing. ZES should be suspected in patients who present with persistent or complex duodenal or postsurgical ulcer, especially if accompanied by esophagitis, diarrhea, weight loss, and/or liver metastases. Twenty percent of ZES patients have multiple endocrine neoplasia type I, some of whom may also have elevated levels of serum calcium and a family history of ZES. Diagnostic tests include fasting serum gastrin concentration, gastric secretion analysis, with, if necessary, secretin stimulation of serum gastrin. Complete surgical tumorectomy for cure is impossible in as many as 70-90% of patients with ZES, who then require long-term medical therapy to reduce acid exposure. Basal acid output needs to be maintained at < 5 mEq/h for uncomplicated ZES and at < 1-2 mEq/h for complicated ZES or postgastrectomy. Proton pump inhibitors (omeprazole, lansoprazole) with careful clinical monitoring provide safe and effective acid control in patients with ZES.

Publication Types:

- Review
- Review, Tutorial

PMID: 9127626 [PubMed - indexed for MEDLINE]

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☐ 30: Am J Gastroenterol 1997 Apr;92(4 Suppl):30S-34S;  
discussion 34S-35S

[Related Articles](#), [NEW Books](#), [LinkOut](#)

### **Long-term management of gastroesophageal reflux disease and its complications.**

Richter JE.

Department of Gastroenterology, Cleveland Clinic Foundation, Ohio 44195, USA.

Although gastroesophageal reflux disease (GERD) is believed to be primarily a motor disorder, current medical therapy is based on the inhibition of acid secretion, since it is the deleterious effects of the acidic refluxate that lead to the symptoms and complications of GERD. Goals of long-term management include the relief of symptoms, healing of esophagitis and prevention of its relapse, and prevention of complications with safe, cost-effective therapy. Maintenance therapy depends on disease severity. Prokinetic drugs have a limited role except in symptomatic nonerosive GERD. Likewise, H<sub>2</sub>-receptor antagonists are useful in relapsing, nonerosive GERD or in cases of mild initial esophagitis. For severe reflux esophagitis, even high doses of H<sub>2</sub>-receptor antagonists do not appear to be as effective as proton pump inhibitors. GERD patients with severe reflux esophagitis or complications such as peptic stricture or Barrett's esophagus should be maintained on

proton pump inhibitors such as lansoprazole or omeprazole. For young and otherwise healthy patients, antireflux surgery is a viable option.

Publication Types:

- Review
- Review, Tutorial

PMID: 9127624 [PubMed - indexed for MEDLINE]

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☐ 31: Am J Gastroenterol 1997 Apr;92(4 Suppl):22S-27S;  
discussion 27S-29S

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### **Therapeutic approaches to healing esophagitis.**

**Boyce HW.**

Department of Internal Medicine, University of South Florida College of Medicine, Tampa 33612, USA.

Medical therapy for reflux esophagitis is designed to provide symptom relief and esophageal healing, and to prevent complications. Life-style modifications serve as an adjunct to drug therapy. Sucralfate, prokinetic agents, and H<sub>2</sub>-receptor antagonists promote symptom relief and esophageal healing in mild esophagitis, but are less effective in the treatment of moderate to severe esophagitis. For patients with mild to severe (erosive) esophagitis, rapid symptom relief and esophageal healing have been achieved with proton pump inhibitors such as omeprazole and lansoprazole.

Publication Types:

- Review
- Review, Tutorial

PMID: 9127623 [PubMed - indexed for MEDLINE]

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☐ 32: Am J Gastroenterol 1997 Apr;92(4 Suppl):17S-19S;  
discussion 19S-21S

[Related Articles](#), [NEW Books](#), [LinkOut](#)

### **Optimizing the pharmacology of acid control in acid-related disorders.**

**Howden CW.**

Department of Internal Medicine, University of South Carolina School of Medicine, Columbia 29203-6808, USA.

Clinical evidence supports the relationship between acid suppression and healing of duodenal ulceration and reflux esophagitis. In contrast to H<sub>2</sub>-receptor antagonists which suppress acid secretion by inhibiting the initial stimulation of the parietal cell, proton pump inhibitors directly inhibit hydrogen ion secretion and can, therefore, better provide the degree and duration of intragastric pH elevation necessary for the optimal management of duodenal ulceration and reflux esophagitis. Clinical studies have shown that proton pump inhibitors, such as omeprazole and lansoprazole, provide more rapid healing and higher healing rates for both duodenal ulcers and reflux esophagitis than do H<sub>2</sub>-receptor antagonists.

Publication Types:

- Review
- Review, Tutorial

PMID: 9127622 [PubMed - indexed for MEDLINE]

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☐ 33: Am Fam Physician 1997 Jan;55(1):205-12, 217-8

[Related Articles](#), [NEW Books](#), [LinkOut](#)

### **Contemporary medical therapy for gastroesophageal reflux disease.**

**Fass R, Hixson LJ, Ciccolo ML, Gord n P, Hunter G, Rappaport W.**

University of Arizona Health Sciences Center, Tucson, USA.

Gastroesophageal reflux disease is a chronic disorder that requires long-term therapy in most patients. The appropriate medical therapy should be individualized to the severity of symptoms, the degree of esophagitis and the presence of other acid-reflux complications. Lifestyle changes should form the basis of any therapeutic approach. In patients with mild to moderate disease, initial therapy with histamine H<sub>2</sub>-receptor antagonists in conventional dosages is suggested. Prokinetic agents are potentially useful in patients with impaired esophageal or gastric motor function, but their efficacy as single agents does not appear to surpass that of standard doses of H<sub>2</sub> blockers. Sucralfate, a cytoprotective agent, is an additional therapeutic option. For patients with more severe disease, omeprazole and lansoprazole provide unequalled healing rates and accelerated symptom relief. In most patients, maintenance therapy is vital. Surgery is indicated in patients whose disease is refractory to medical therapy and in those who develop complications not amenable to medical therapy.

Publication Types:

- Review
- Review, Tutorial

PMID: 9012279 [PubMed - indexed for MEDLINE]

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☐ 34: Fortschr Med 1996 Dec 20;114(35-36):497-9

Related Articles, **NEW** Books, LinkOut

**[Helicobacter pylori eradication: modified triple therapy with lansoprazole]**

[Article in German]

**Muller P, Simon B.**

Innere Abteilung, Krankenhaus Salem, Heidelberg.

For the eradication of *Helicobacter pylori* in H.p.-positive patients with peptic ulcer, preference is presently being given worldwide to the modified triple therapy-comprising an acid suppressant and two antibiotics. This relatively new form of treatment is highly effective, relatively well tolerated, patient-friendly (5 to 6 tablets daily), and inexpensive. In 12 studies involving more than 600 patients, the new proton pump inhibitor, lansoprazole, has proved to be an effective component of this eradication regimen. In combination with clarithromycin and metronidazole or amoxicillin and clarithromycin, consistently high eradication rates of more than 85% are obtained, with treatment of only seven days duration. Since in terms of clinical efficacy 30 mg lansoprazole daily presumably correspond to 40 mg omeprazole daily, the new proton pump inhibitor represents a more economic alternative for H.p. eradication.

Publication Types:

- Review
- Review, Tutorial

PMID: 9119351 [PubMed - indexed for MEDLINE]

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☐ 35: Presse Med 1996 Dec 14;25(39):1917-22

Related Articles, **NEW** Books, LinkOut

**[The treatment of Helicobacter pylori infection]**

[Article in French]

**de Korwin JD, Lozniewski A.**

Service de Medecine D, Hopital Central, CHU, Nancy.

*H. pylori* causes inflammatory lesions of the stomach and duodenum. At the present time eradication is essentially recommended in case of gastric or duodenal ulcer. The choice of the appropriate drug depends on the characteristics of the *H. pylori* infection, the localization deep in the gastric mucosa, the physico-chemical properties of the gastric medium, especially the acidity which deactivates antibiotics, slow bacterial growth and the germ's sensitivity to antibiotics. Anti-infectious treatment is now based on a three-drug regimen combining an antisecretory drug (proton pump inhibitor or H<sub>2</sub> receptor antagonist) and two antibiotics: clarithromycin associated with amoxicillin or an imidazol derivative (metronidazol or tinidazol) or tetracycline. Two antibiotics (clarithromycin, amoxicillin) as well as three anti-secretory agents (lansoprazole, omeprazole, ranitidine) have been

authorized in France for three-drug regimens of 1 or 2 weeks leading to approximately 90% eradication. Special attention should be placed on the risk of resistance to antibiotics (macrolids and imidazol derivatives) and patient compliance required for successful eradication of *H. pylori*. Other therapeutic schemes are under assessment and a vaccine is being prepared. Eradication of *H. pylori* has totally changed the treatment of gastric and duodenal ulcers, eliminating the need for long-term treatment and avoiding complications.

Publication Types:

- Review
- Review, Tutorial

PMID: 9033612 [PubMed - indexed for MEDLINE]

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☐ 36: Ann Pharmacother 1996 Dec;30(12):1425-36

Related Articles, **NEW** Books, LinkOut

**Lansoprazole: a proton pump inhibitor.**

**Garnett WR.**

Department of Pharmacy and Pharmaceuticals, School of Pharmacy, Medical College of Virginia, Virginia Commonwealth University, Richmond 23298, USA.

**OBJECTIVE:** To summarize the published data on lansoprazole, a proton pump inhibitor approved by the Food and Drug Administration for use in the treatment of duodenal ulcer, erosive esophagitis, and pathologic hypersecretory conditions (e.g., Zollinger-Ellison syndrome). **DATA SOURCES:** Published data on lansoprazole identified by MEDLINE searches (1985-1996), as well as other pertinent literature. **STUDY SELECTION:** Clinical efficacy trials discussed were limited to multicenter, double-blind, parallel group, prospective studies, where possible. **DATA SYNTHESIS:** Lansoprazole inhibits gastric acid secretion via inhibition of gastric hydrogen/potassium adenosine triphosphatase ( $H^+,K^+-ATPase$ ), an enzyme of the gastric parietal cell membrane that forms part of the proton pump that performs the final step in the acid secretory process. Lansoprazole binds covalently to parietal cell  $H^+,K^+-ATPase$ , rendering it nonfunctional and inhibiting the secretion of gastric acid. In clinical trials, lansoprazole has been shown to be more effective than placebo and standard doses of histamine ( $H_2$ )-receptor antagonists and as effective as standard doses of omeprazole for the treatment of peptic ulcer disease, gastroesophageal reflux, Zollinger-Ellison syndrome, and nonsteroidal antiinflammatory drug-induced lesions. **CONCLUSIONS:** Lansoprazole is safe and effective for the treatment of acid-related disorders. It is more effective than the  $H_2$ -receptor antagonists and comparable to omeprazole for these indications. The choice between lansoprazole and omeprazole is likely to be institution-specific and pharmacoeconomic.

Publication Types:

- Review
- Review, Tutorial

PMID: 8968456 [PubMed - indexed for MEDLINE]

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☐ 37: Clin Pharmacokinet 1996 Nov;31(5):386-406

Related Articles, **NEW** Books, LinkOut

**Pharmacokinetic optimisation in the treatment of gastro-oesophageal reflux disease.**

**Hatlebakk JG, Berstad A.**

Medical Department A, Haukeland Hospital, University of Bergen, Norway.

Gastro-oesophageal reflux disease (GORD) is a very common disorder of upper gastro-intestinal motility, differing widely in severity and prognosis. Medical therapy of GORD has involved antacids, alginates, prokinetic agents and antisecretory compounds, primarily  $H_2$  receptor antagonists and proton pump inhibitors. Knowledge of the pharmacokinetics of these compounds is important, to optimise the therapeutic benefit in each patient. GORD patients are often elderly and pharmacokinetics are more variable in this group. Furthermore, they often suffer from other diseases needing medical therapy and may need a combination of drugs to heal reflux oesophagitis and relieve reflux symptoms. The ideal therapy for GORD will have linear pharmacokinetics, a relatively long plasma half-life ( $t_{1/2}$ ), a duration of action allowing once daily administration, and a stable effect independent of interactions with food, antacids and other drugs. Over-the-counter antacids and alginates are widely used, but may affect absorption of  $H_2$  receptor antagonists like

cimetidine and ranitidine. Aluminium-containing antacids may, over time, cause toxicity in patients with renal insufficiency. In the treatment of GORD, cisapride presents important advantages over earlier prokinetic compounds, with a longer plasma  $t_{1/2}$ , low penetration of the blood-brain barrier and fewer adverse effects. The group of H<sub>2</sub> receptor antagonists is still the most frequently used therapy for GORD. Linear pharmacokinetics make dose adjustments easy and safe. In individual patients, suppression of gastric secretion is related to the area under the plasma concentration-time curve (AUC), but there is wide interindividual variation in the effect of the same oral dose. Only with frequent administration and high doses will acid suppression approximate that of proton pump inhibitors. Tolerance, with loss of effect over time, however, is most pronounced in this situation. H<sub>2</sub> receptor antagonists seem well suited for on-demand treatment of reflux symptoms, due to the rapid onset of effect and a decreased likelihood of the development of tolerance. Effervescent formulations provide more rapid absorption and almost immediate clinical effect. Cimetidine, however, causes interference with the metabolism of several other drugs in common use. In elderly patients elimination is delayed and in patients with renal insufficiency, dose reductions of all H<sub>2</sub> receptor antagonists are recommended. The most effective medical therapy for any severity of GORD, particularly in severe oesophagitis, are the proton pump inhibitors. The substituted benzimidazoles (omeprazole, lansoprazole and pantoprazole), are prodrugs which once trapped and activated in the acid milieu of the gastric glands potently suppress gastric secretion of acid and pepsin. Their long duration of action, more related to the slow turnover of parietal cell H<sup>(+)</sup>-K<sup>+</sup> ATPase molecules, allows once daily administration in most patients. Interindividual variation in bioavailability sometimes calls for higher doses or twice daily administration. Acid suppression is closely related to the AUC. Omeprazole is prone to interaction with the metabolism of other drugs, some of which may be clinically important. Lansoprazole seems to have an earlier onset of action than omeprazole, ascribed to higher bioavailability during the first days of treatment. Proton pump inhibitors have a slow onset of action, which makes them unsuited for on-demand therapy. Clinical practice in GORD calls for the use of not one but several substances, according to the severity and symptom pattern of the patient. Pharmacokinetic optimisation in the treatment of GORD is a question of selecting the most suitable substances and administration schemes within each group. Cisapride is superior to other prokinetics in terms of longer plasma  $t_{1/2}$  and less toxicity. Amongst H<sub>2</sub> receptor antagonists, the more long-acting compounds, ranitidine and famotidine, will improve acidity control througho

Publication Types:

- Review
- Review, Academic

PMID: 9118586 [PubMed - indexed for MEDLINE]

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☐ 38: Clin Pharmacokinet 1996 Jul;31(1):9-28

Related Articles, **NEW** Books, LinkOut

Erratum in:

- Clin Pharmacokinet 1996 Oct;31(4):274

**Pharmacokinetics, metabolism and interactions of acid pump inhibitors.  
Focus on omeprazole, lansoprazole and pantoprazole.**

**Andersson T.**

Astra Hassle, Molndal, Sweden.

This review updates and evaluates the currently available information regarding the pharmacokinetics, metabolism and interactions of the acid pump inhibitors omeprazole, lansoprazole and pantoprazole. Differences and similarities between the compounds are discussed. Omeprazole, lansoprazole and pantoprazole are all mainly metabolised by the polymorphically expressed cytochrome P450 (CYP) isoform S-mephenytoin hydroxylase (CYP2C19), which means that within a population a few individuals (3% of Caucasians) metabolise the compounds slowly compared with the majority of the population. For all 3 compounds, the area under the plasma concentration-versus-time curve (AUC) for a slow metaboliser is, in general, approximately 5 times higher than that in an average patient. Since all 3 compounds are considered safe and well tolerated, and no dosage-related adverse drug reactions have been identified, this finding seems to be of no clinical relevance. The acid pump inhibitors seem to be similarly handled in the elderly, where a somewhat slower elimination can be demonstrated compared with young individuals. In patients with renal insufficiency, omeprazole is eliminated as in healthy individuals, whereas the data on lansoprazole and pantoprazole are unresolved. In patients with hepatic insufficiency, as expected, the elimination rates of all 3 compounds are substantially decreased. No clinically relevant effects on specific endogenous glandular functions, such as the adrenal (cortisol), the gonads or the thyroid, were demonstrated for omeprazole and pantoprazole, whereas a few minor concerns have been raised regarding lansoprazole. The absorption of some compounds, e.g. digoxin, might be altered as a result of the increased gastric pH obtained during treatment with acid pump inhibitors, and, accordingly, similar

effects are expected irrespective of which acid pump inhibitor is given. The effect of the acid pump inhibitors on enzymes in the liver has been intensely debated, and some authors have claimed that lansoprazole and pantoprazole have less potential than omeprazole to interact with other drugs metabolised by CYP. However, after assessment of available data in this area, the conclusion is that all 3 acid pump inhibitors have a very limited potential for drug interactions at the CYP level. In addition, the small effects on CYP reported for these compounds are rarely of any clinical relevance, considering the normal intra- (and inter-)individual variations in metabolism observed for most drugs. In conclusion, omeprazole, lansoprazole and pantoprazole are structurally very similar, and an evaluation of available data indicates that also with respect to pharmacokinetics, metabolism and interactions in general they demonstrate very similar properties, even though omeprazole has been more thoroughly studied with regard to different effects.

Publication Types:

- Review
- Review, Tutorial

PMID: 8827397 [PubMed - indexed for MEDLINE]

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☐ 39: Drugs 1996 Jul;52(1):33-44

Related Articles, **NEW** Books, LinkOut

**Zollinger-Ellison syndrome. Recognition and management of acid hypersecretion.**

**Maton PN.**

Oklahoma Foundation for Digestive Research, Oklahoma City, USA.

Zollinger-Ellison syndrome (ZES) should be suspected if a patient has severe peptic ulceration, ulcers and kidney stones, a family history of ulcers or endocrine diseases, watery diarrhoea or malabsorption with or without ulcers, or if hypergastrinaemia is found. Any patient in whom ZES is suspected, and certainly if diagnosed, should be given large doses of antisecretory medication immediately. This should never be stopped except under controlled conditions or unless acid outputs have been reduced surgically. Patients cannot be managed safely without measuring acid outputs. These should be lowered to < 10 mmol/h, or < 5 mmol/h in patients with a previous gastric resection or severe oesophageal disease. Acid secretion can be controlled acutely in 70% of patients with an infusion of ranitidine 1 mg/kg/h, while 4 mg/kg/h will control acid in all. The initial oral dosage of omeprazole or lansoprazole should be 60 mg/day. Doses should then be adjusted daily on the basis of acid outputs. Proton pump inhibitors in a dosage of 60 mg/day will control acid output in most patients and 60 mg every 12 hours will control acid output in all. Doses can then often be slowly and progressively reduced. A parietal cell vagotomy reduces acid secretion and reduces, but does not abolish, the need for antisecretory medication. In patients with multiple endocrine neoplasia type 1 and hyperparathyroidism, a parathyroidectomy that results in normocalcaemia will reduce acid secretion and drug requirements. A total gastrectomy is rarely if ever needed nowadays. Given the high degree of safety of gastric antisecretory medications versus the risks of acid hypersecretion in patients with ZES, the mistakes in management of acid hypersecretion that must be avoided are those of giving insufficient medication and not measuring acid secretory rates.

Publication Types:

- Review
- Review, Tutorial

PMID: 8799683 [PubMed - indexed for MEDLINE]

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☐ 40: Am J Health Syst Pharm 1996 Jun 15;53(12):1401-15

Related Articles, **NEW** Books, LinkOut

Comment in:

- Am J Health Syst Pharm. 1996 Dec 1;53(23):2882, 2884.

**Lansoprazole and omeprazole in the treatment of acid peptic disorders.**

**Blum RA.**

State University of New York at Buffalo, USA.

The pharmacology, pharmacokinetics, efficacy, safety, and dosage and administration of lansoprazole and omeprazole are reviewed. Lansoprazole and omeprazole are

proton-pump inhibitors (PPIs). These agents bind covalently to hydrogen/potassium-exchanging adenosine triphosphatase in gastric parietal cells, rendering the molecule nonfunctional and inhibiting the secretion of gastric acid. The bioavailability of lansoprazole is 85%; that of omeprazole is 54%. Although lansoprazole and omeprazole have a plasma half-life of less than 2 hours, the duration of action is more than 24 hours. Clinical trials have shown lansoprazole and omeprazole to be effective in the treatment of duodenal ulcers, gastric ulcers, peptic ulcer disease involving *Helicobacter pylori* infection, recurrent ulcers, ulcers induced by nonsteroidal anti-inflammatory drugs, reflux esophagitis, Barrett esophagus, and Zollinger-Ellison syndrome. In many cases, these PPIs were more effective than histamine H2-receptor antagonists or worked when the latter failed. Lansoprazole and omeprazole have similar adverse-effect profiles and are well tolerated in both long- and short-term therapy. The dosage and duration of therapy vary with the condition being treated or the individual patient. Dosage adjustments should be considered only in the case of lansoprazole in patients with severe liver disease. Lansoprazole and omeprazole are highly specific in blocking a critical step in gastric acid production and have been found to be safe and effective in the treatment of many acid peptic disorders.

Publication Types:

- Review
- Review, Academic

PMID: 8781686 [PubMed - indexed for MEDLINE]

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☐ 41: Drugs 1996 Mar;51(3):460-82

Related Articles, **NEW** Books, LinkOut

Erratum in:

- Drugs 1996 Jul;52(1):92
- Drugs 1996 Jun;51(6):1074

**Pantoprazole. A review of its pharmacological properties and therapeutic use in acid-related disorders.**

Fitton A, Wiseman L.

Adis International Limited, Auckland, New Zealand.

Pantoprazole is an irreversible proton pump inhibitor which, at the therapeutic dose of 40mg, effectively reduces gastric acid secretion. In controlled clinical trials, pantoprazole (40mg once daily) has proved superior to ranitidine (300mg once daily or 150mg twice daily) and equivalent to omeprazole (20mg once daily) in the short term (< or = 8 weeks) treatment of acute peptic ulcer and reflux oesophagitis. Gastric and duodenal ulcer healing proceeded significantly faster with pantoprazole than with ranitidine, and at similar rates with pantoprazole and omeprazole. The time course of gastric ulcer pain relief was similar with pantoprazole, ranitidine and omeprazole, whereas duodenal ulcer pain was alleviated more rapidly with pantoprazole than ranitidine. Pantoprazole (40mg once daily) showed superior efficacy to famotidine (40mg once daily) in ulcer healing and pain relief after 2 weeks in patients with duodenal ulcer in a large multicentre nonblinded study. In mild to moderate acute reflux oesophagitis, significantly greater healing was obtained with pantoprazole than with ranitidine and famotidine, whereas similar healing rates were seen with pantoprazole and omeprazole. Pantoprazole showed a significant advantage over ranitidine in relieving symptoms of heartburn and acid regurgitation. Reflux symptoms were similarly alleviated by pantoprazole and omeprazole. Preliminary results indicate that triple therapy with pantoprazole, clarithromycin and either metronidazole or tinidazole is effective in the treatment of *Helicobacter pylori*-associated disease; however, these findings require confirmation in large well-controlled studies. Pantoprazole appears to be well tolerated during short term oral administration, with diarrhoea (1.5%), headache (1.3%), dizziness (0.7%), pruritus (0.5%) and skin rash (0.4%) representing the most frequent adverse events. The drug has lower affinity than omeprazole or lansoprazole for hepatic cytochrome P450 and shows no clinically relevant pharmacokinetic or pharmacodynamic interactions at therapeutic doses with a wide range of drug substrates for this isoenzyme system. In conclusion, pantoprazole is superior to ranitidine and as effective as omeprazole in the short term treatment of peptic ulcer and reflux oesophagitis, has shown efficacy when combined with antibacterial agents in *H. pylori* eradication, is apparently well tolerated and offers the potential advantage of minimal risk of drug interaction.

Publication Types:

- Review
- Review, Tutorial

PMID: 8882382 [PubMed - indexed for MEDLINE]

☐ 42: Clin Pharmacokinet 1995 Jun;28(6):458-70Related Articles, **NEW** Books, LinkOut**Clinical pharmacokinetics of lansoprazole.****Landes BD, Petite JP, Flouvat B.**

Toxicology and Pharmacokinetics Laboratory, Ambroise Pare Hospital, Boulogne, France.

Lansoprazole, a benzimidazole derivative with antisecretory and antiulcer activities, inhibits the acid pump activity at the final stage of the enzyme process and therefore reduces the acid secretion of parietal cells. Lansoprazole is converted to active metabolites in the acid environment of these cells. It is rapidly absorbed from a gastric acid-resistant formulation and is approximately 97% bound in human plasma. Single dose pharmacokinetics of lansoprazole appear to be linear over the range from 15 to 60mg. Food and time of dose influence absorption after single doses, but do not modify the antisecretory effect of multiple doses. Lansoprazole is extensively metabolised following oral administration into sulphone and 5-hydroxylated metabolites by the cytochrome P450 enzymes CYP3A4 and CYP2C18. Two other metabolites have been identified in plasma: sulphide and hydroxylated sulphone. Mean plasma elimination half-life ( $t_{1/2}$ ) is between 1.3 and 2.1 hours in healthy volunteers. 15 to 23% of the total dose is found in urine as free and conjugated hydroxylated metabolites, while unchanged lansoprazole is not detected. The pharmacokinetic profile of the drug is not modified by multiple administration. In healthy elderly volunteers, area under the plasma concentration-time curve (AUC) and  $t_{1/2}$  are significantly greater after single administration occurs to the same extent as in young volunteers. Renal failure has no influence on the pharmacokinetics of lansoprazole, but severe hepatic failure causes a significant decrease in clearance and an increase in the AUC and  $t_{1/2}$  of lansoprazole. This is accompanied by modifications in the AUC of metabolites, but severe hepatic failure has minimal effect on accumulation of the drug after multiple administration. The pharmacokinetics of lansoprazole in patients with acid-related disorders do not differ from those in healthy volunteers. Studies of interactions of lansoprazole with warfarin, prednisone, theophylline, phenazone (antipyrine), diazepam, phenytoin and oral contraceptives suggest minimal risk of any clinically significant interaction.

## Publication Types:

- Review
- Review, Tutorial

PMID: 7656504 [PubMed - indexed for MEDLINE]

☐ 43: Gan To Kagaku Ryoho 1995 Feb;22(2):169-78Related Articles, **NEW** Books, LinkOut**[Helicobacter pylori in peptic ulcer and gastric cancer]**

[Article in Japanese]

**Matsukura N, Onda M, Yamashita K.**

First Dept. of Surgery, Nippon Medical School.

Recently many reports have shown a strong association between *Helicobacter pylori* infection in the stomach and recurrent peptic ulcer. Moreover, prospective cohort serological studies showed that *H. pylori* infected individuals have significantly increased rate of gastric cancer in the USA. *H. pylori* is a gram-negative spiral organism which has urease activity and produces ammonia and CO<sub>2</sub> from urea, and nestles in the gastric pits and overlying mucus gel layer. Many diagnostic methods of *H. pylori* infection are available; ie bacterial culture, <sup>13</sup>C-urea breath test, histology, serum IgG antibody against *H. pylori*. We developed a new method, ie tissue IgA antibody against *H. pylori* and detection of *H. pylori* DNA in the gastric juice by PCR method. Triple therapies with metronidazole, bismuth compounds, and amoxicillin or tetracyclin are difficult to use in Japan because of their severe side effects. Thus, new methods with proton pump inhibitor (PPI) and amoxicillin have been introduced. We treated 14 patients of whom were *H. pylori* positive-active peptic ulcer with 30 mg/day of lansoprazole, a new PPI, plus 1,500 mg/day of amoxicillin for 2 weeks and 8 (57%) patients were eradicated. Gastric carcinogenesis are multi-steps and multifactorials process. Hypothetical sequence of intestinal type of gastric cancer is that superficial gastritis-->atrophic gastritis-->intestinal metaplasia-->dysplasia-->gastric cancer and *H. pylori* infection may play a role in the early stage of the sequence. We examined mucosal IgA antibody against *H. pylori* in chronic gastritis and intestinal metaplasia detected by the Tes-Tape method in 25 resected specimens after gastrectomy for gastric cancer. Positivity rates of tissue *H. pylori* IgA antibody were lower in the mucosa of intestinal metaplasia than in non-metaplastic gastric mucosa and were negative in carcinoma. Causal relationship



between *H. pylori* infection and gastric cancer is not proven and factors other than *H. pylori* infection are also important in the gastric carcinogenesis. Finally we introduce 2 reports: (1) NIH Consensus Conference: *Helicobacter pylori* in peptic ulcer disease (JAMA. 1994; 272: 65-69). The consensus panel concluded that 1. ulcer patients with *H. pylori* infection require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation with the illness or on recurrence; 2. the value of treating nonulcerative dyspepsia patients with *H. pylori* infection remains to be determined; and 3. the interesting relationship between *H. pylori* infection and gastric cancer requires further exploration. (2) World Health Organization: Working Group Meeting (Reported in World Congress of Gastroenterology, Los Angeles, 1994). *H. pylori* plays a causal role in the chain of events leading to cancer of the stomach. Group I: definite carcinogen.

Publication Types:

- Review
- Review, Tutorial

PMID: 7857088 [PubMed - indexed for MEDLINE]

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☐ 44: Digestion 1995;56(6):443-54

Related Articles, **NEW** Books, LinkOut

**Similarities and differences in the properties of substituted benzimidazoles: a comparison between pantoprazole and related compounds.**

Kromer W.

Department of Pharmacology, Byk Gulden, Konstanz, Germany.

The novel antiulcer drugs omeprazole, lansoprazole, and pantoprazole are members of the class of substituted benzimidazoles. They potently inhibit the gastric proton pump by a common mechanism which depends on the acid-induced conversion of the parent compounds to the pharmacologically active principles: thiophilic cyclic sulfenamides. This transformation takes place in the luminal compartment of the secreting parietal cell. However, while the three proton pump inhibitors belong to the same chemical class, their two ring systems bear different functional substituents. This leads to essential modification of the physiochemical, metabolic, and pharmacokinetic properties of these drugs, possibly resulting in differences in tissue selectivity and thereby, in the long term, drug safety. Both preclinical and clinical data have accumulated that point to advantages of pantoprazole related to the above parameters: pantoprazole shows a higher stability at moderately acidic pH values and less inhibitory potential against cytochrome P450 than the other two drugs. In addition, pantoprazole displays linear pharmacokinetics with a high bioavailability.

Publication Types:

- Review
- Review, Academic

PMID: 8536813 [PubMed - indexed for MEDLINE]

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☐ 45: J Clin Gastroenterol 1995;20 Suppl 1:S43-7

Related Articles, **NEW** Books, LinkOut

**The potential value of lansoprazole in *Helicobacter pylori* eradication.**

Axon AT.

Centre for Digestive Diseases, General Infirmary at Leeds, England.

Most anti-*Helicobacter pylori* (Hp) regimens available have drawbacks. Standard triple therapy using bismuth, metronidazole, and tetracycline gives good eradication rates but at the expense of a long, complicated regimen associated with significant side effects, and results are not as good in areas where there is a high resistance to nitroimidazoles. The introduction of eradication regimens based on acid suppression in combination with antibiotics has yielded promising results. Dual therapy using a proton pump inhibitor (PPI) with either amoxicillin or clarithromycin has yielded eradication rates above 80% with relatively few side effects, but results have been somewhat inconsistent from center to center. The combination of acid suppression with two antibiotics has provided better results, with centers achieving eradication rates of over 90%. The new PPI lansoprazole possesses some theoretical advantages as an acid-suppressing drug, and its preliminary use in a number of studies suggests that it may have an important role to play in Hp eradication regimens. Considerably more work, however, is required to identify the ideal dosage and combination that will give the best eradication rates with the simplest regimen and fewest

side effects.

Publication Types:

- Review
- Review, Tutorial

PMID: 7673614 [PubMed - indexed for MEDLINE]

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☐ 46: J Clin Gastroenterol 1995;20 Suppl 1:S28-31

[Related Articles](#), [NEW Books](#), [LinkOut](#)

**Adjuvant therapy for Helicobacter pylori eradication: role of lansoprazole in clinical studies.**

Lamouliatte H.

Hopital Saint-Andre, Bordeaux, France.

Helicobacter pylori (Hp) eradication can lead to cure of duodenal ulcer. Eradication of Hp was first attempted with bismuth salts alone or in combination with one or two antibiotics. In 1990, triple therapy with bismuth, tetracycline or amoxicillin, and metronidazole or tinidazole was standard. Proton pump inhibitors are active in vitro against Hp and have therefore been tested in monotherapy, dual therapy, and triple therapy. When lansoprazole was used as monotherapy, the mean Hp eradication was 6% in four studies. When lansoprazole was used in dual therapy with amoxicillin, pooled data from four trials employing various dosage schedules showed Hp eradication in 38.9% of patients. When lansoprazole was used in dual therapy with clarithromycin, the eradication rate was about 47.7% with lansoprazole 30 mg daily and 69.1% with lansoprazole 30 mg twice daily. When lansoprazole was used in triple therapy, Hp eradication rates ranged from 80% to 96%, with the best results obtained with a combination of lansoprazole, amoxicillin, and clarithromycin. Lansoprazole together with one or preferably two antibiotics is effective in Hp eradication. With the new macrolides, which have a lower rate of Hp resistance than metronidazole or tinidazole, we can expect to achieve eradication of Hp in all patients who are compliant with antibiotic therapy and infected with sensitive strains.

Publication Types:

- Review
- Review, Tutorial

PMID: 7673611 [PubMed - indexed for MEDLINE]

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☐ 47: Annu Rev Pharmacol Toxicol 1995;35:277-305

[Related Articles](#), [NEW Books](#), [LinkOut](#)

**The pharmacology of the gastric acid pump: the H<sup>+</sup>,K<sup>+</sup> ATPase.**

Sachs G, Shin JM, Briving C, Wallmark B, Hersey S.

Department of Medicine and Physiology, Wadsworth VA Hospital, Los Angeles, California 90073, USA.

The gastric H<sup>+</sup>,K<sup>+</sup> ATPase--the gastric acid pump--is the molecular target for the class of antiseecretory drugs called the proton-pump inhibitors (PPIs). These compounds--omeprazole, lansoprazole, and pantoprazole--contain, as their core structure, 2-pyridyl methylsulfinyl benzimidazole. The H<sup>+</sup>,K<sup>+</sup> ATPase is a heterodimer composed of a 1034-amino acid catalytic alpha peptide and a glycosylated 291-amino acid beta subunit. The alpha subunit probably contains 10 membrane-spanning sequences; the beta, a single transmembrane segment. The PPIs have a pKa of about 4.0; hence they accumulate only in the acidic secretory canaliculus of the stimulated parietal cell. Here they undergo conversion to a cationic sulfenamide, which then reacts with available cysteines on the extracytoplasmic face of the alpha subunit. Omeprazole reacts and forms disulfide bonds with cys813(822) and cys892; lansoprazole, with cys813(822), cys892, and cys321; and pantoprazole, with cys813 and -822. The antiseecretory effect of the drugs reflects their short plasma half-life (approximately 60 min), the number of active pumps during that time, and the recovery of pumps following biosynthesis and reversal of inhibition. These drugs also show synergism with either amoxicillin or clarithromycin in eradicating Helicobacter pylori, an organism shown to be important in duodenal and gastric ulcer disease. Their action is probably due to elevation of pH in the environment of the organism, rather than to any direct action.

Publication Types:

- Review
- Review, Tutorial

PMID: 7598495 [PubMed - indexed for MEDLINE]

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**48: Aliment Pharmacol Ther 1995;9 Suppl 1:39-42**[Related Articles](#), [NEW Books](#), [LinkOut](#)**No *Helicobacter pylori*, no *Helicobacter pylori*-associated peptic ulcer disease.****Tytgat GN.**

Academic Medical Centre, Department of Gastroenterology &amp; Hepatology, Amsterdam, The Netherlands.

Virtually all duodenal ulcers (DUs) and the vast majority of gastric ulcers (GUs) are the consequence of *Helicobacter pylori*-associated inflammation. In DUs, the inflammation is maximal in the antrum and is associated with gastric metaplasia in the bulb. Gastrin homeostasis is disturbed by *H. pylori* gastritis and there is robust acid secretion. Successful eradication of the infection cures the ulcer diathesis. Amalgamated figures for ulcer relapse per year in *H. pylori*-positive DUs are > 60% compared with 2.6% for *H. pylori*-negative DU patients. The corresponding figures for GU are > 50% for *H. pylori*-positive and 2.0% for *H. pylori*-negative individuals. This striking difference in relapse rate persists, as the re-infection rate in the developed world is < 1% per year. Recurrent bleeding in bleeding-prone DUs is essentially abolished after cure of the infection. Proton pump inhibitors (PPIs) are increasingly used in eradication regimens. PPIs have intrinsic antimicrobial activity. MICs for lansoprazole (LAN) are lower than for omeprazole (OME). Two weeks of triple therapy (bismuth, tetracycline, imidazole) has, on average, a superior eradication efficacy (> or = 90%) compared with dual therapy (PPI, amoxycillin or clarithromycin) (> or = 80%). When a combination of PPI and two antibiotics has been used, results comparable to triple therapy have been reported. However, the side-effects profile and patient acceptability of PPI plus one or two antibiotic regimens are better than for traditional triple therapy. (ABSTRACT TRUNCATED AT 250 WORDS)

**Publication Types:**

- Review
- Review, Tutorial

PMID: 7495941 [PubMed - indexed for MEDLINE]

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**49: Clin Pharmacokinet 1994 Nov;27(5):393-408**[Related Articles](#), [NEW Books](#), [LinkOut](#)**Pharmacokinetic optimisation of the treatment of peptic ulcer in patients with renal failure.****Gladziwa U, Koltz U.**

Department of Internal Medicine II, Technical University, Aachen, Germany.

The pathogenesis of peptic ulceration is not yet clear. It could be due to an imbalance between acid secretion and mucosal defensive and/or protective mechanisms, but the association between *Helicobacter pylori* and peptic ulceration has questioned this hypothesis. Therefore, drugs inhibiting acid secretion and/or eradicating *H. pylori* are of major interest. Peptic ulcer disease is often associated with renal failure. For the selection of the proper dosage of these agents their pharmacokinetic properties and alterations in pharmacokinetics in various disease states, including renal failure, should be known. As histamine H2-receptor antagonists and pirenzepine are mainly eliminated by the renal route their elimination is dependent on creatinine clearance. Consequently, their elimination will be impaired in patients with renal insufficiency, which makes dosage reduction mandatory in these patients. No dosage supplementation is necessary after any type of dialysis because the drugs are removed in insignificant amounts by the various blood purification procedures. Misoprostol and proton pump inhibitors, such as omeprazole, lansoprazole and pantoprazole, are primarily eliminated by nonrenal routes. Therefore no dosage adjustments are necessary in patients with renal insufficiency. Bismuth salts, sucralfate and antacids should be avoided in patients with renal failure because of the accumulation of their cations and the associated risk of toxic reactions. For most agents more long term experience from comparative and double-blinded studies is needed to define better their clinical efficacy and tolerability in patients with renal failure.

## Publication Types:

- Review
- Review, Academic

PMID: 7851056 [PubMed - indexed for MEDLINE]

☐ 50: Drugs 1994 Sep;48(3):404-30[Related Articles](#), [NEW Books](#), [LinkOut](#)**Lansoprazole. A reappraisal of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy in acid-related disorders.****Spencer CM, Faulds D.**

Adis International Limited, Auckland, New Zealand.

Lansoprazole is a benzimidazole derivative that effectively decreases gastric acid secretion, regardless of the primary stimulus, via inhibition of gastric H<sup>+</sup>,K<sup>(+)</sup>-adenosine triphosphatase (ATPase). It provides effective symptom relief and healing of peptic ulcer and reflux oesophagitis after 4 to 8 weeks of therapy and appears to prevent recurrence of lesions when administered as maintenance therapy. When administered at therapeutic dosages, lansoprazole produced higher healing rates than ranitidine or famotidine in patients with duodenal and gastric ulcers. Lansoprazole heals duodenal ulcers more rapidly than ranitidine or famotidine. Relief of ulcer symptoms in lansoprazole recipients is at least equivalent to, and tends to be more rapid than, that in patients receiving histamine H<sub>2</sub>-receptor antagonists. In comparisons with omeprazole 20 mg/day, lansoprazole 30 mg/day produced duodenal ulcer healing more rapidly and reduced ulcer pain to a greater extent at 2 weeks, but overall healing rates were similar after 4 weeks of therapy. At therapeutic dosages, lansoprazole produces superior healing and symptom relief of reflux oesophagitis in comparison with ranitidine, and it tends to relieve heartburn more effectively than omeprazole, although both agents produce equivalent healing. Healing of peptic ulcers or reflux oesophagitis refractory to histamine H<sub>2</sub>-receptor antagonists occurs after 8 weeks in the majority of patients treated with lansoprazole, and lansoprazole and omeprazole demonstrate similar efficacy in patients with refractory peptic ulcers. In patients with Zollinger-Ellison syndrome, lansoprazole effectively controls mean basal gastric acid output. Lansoprazole is generally well tolerated in clinical trials. The incidence of adverse effects is similar to that of omeprazole, ranitidine and famotidine in comparative studies. Combination therapy with lansoprazole and antibacterial agents such as amoxicillin, tinidazole, roxithromycin and/or metronidazole appears to eradicate *Helicobacter pylori* in 22 to 80% of patients with this organism. Limited data also suggest that lansoprazole may have superior activity against *H. pylori* in comparison with omeprazole, although the clinical relevance of this preliminary finding requires further confirmation. Thus, lansoprazole may be considered as alternative to existing antisecretory agents available for the treatment of acid-related disorders, particularly because it may provide more rapid healing and relief of symptoms.

## Publication Types:

- Review
- Review, Academic

PMID: 7527761 [PubMed - indexed for MEDLINE]

☐ 51: Drugs 1994 Jul;48(1):91-132[Related Articles](#), [NEW Books](#), [LinkOut](#)**Omeprazole. An update of its pharmacology and therapeutic use in acid-related disorders.****Wilde MI, McTavish D.**

Adis International Limited, Auckland, New Zealand.

Omeprazole, a gastric acid pump inhibitor, dose-dependently controls gastric acid secretion: the drug has greater antisecretory activity than histamine H<sub>2</sub>-receptor antagonists. Omeprazole 20 to 40 mg/day is more effective than histamine H<sub>2</sub>-receptor antagonists in the short term treatment of duodenal ulcer, gastric ulcer and reflux oesophagitis. Available data suggest that omeprazole 10 to 40 mg/day is also more effective than ranitidine in the maintenance therapy of duodenal ulcer and reflux oesophagitis. The drug is also effective in patients with duodenal ulcer, gastric ulcer or reflux oesophagitis poorly responsive to histamine H<sub>2</sub>-receptor antagonists. The efficacy of omeprazole 20 mg/day appears to be similar to that of lansoprazole 30 mg/day in the short term treatment of duodenal ulcer, gastric ulcer and reflux oesophagitis. However, most available studies have been reported

in abstract form only, and 2 of 3 studies in patients with duodenal ulcer have shown greater healing rates at 2 (but not 4) weeks with lansoprazole. Helicobacter pylori eradication decreases duodenal ulcer relapse rates and appears to be associated with improved duodenal ulcer healing rates. Evidence also suggests that H. pylori eradication is associated with reduced gastric ulcer relapse rates. Omeprazole monotherapy may suppress but does not eradicate H. pylori infection. Eradication rates with omeprazole 20 or 40 mg twice daily plus amoxicillin usually up to 2 g/day (3 g/day in a few studies) for 2 weeks appear to be similar to those of standard triple therapy (bismuth salt plus metronidazole, plus tetracycline or amoxicillin) or omeprazole plus clarithromycin, although eradication rates vary widely. Omeprazole plus amoxicillin appears to be better tolerated than triple therapy and represents a first-line treatment alternative in patients with H. pylori-associated peptic ulcer disease. Omeprazole plus amoxicillin plus metronidazole appears to be more effective than omeprazole plus amoxicillin in patients with metronidazole-sensitive H. pylori infection. Omeprazole remains a treatment of choice in patients with Zollinger-Ellison syndrome. The dosages should be adjusted according to individual response. However, relatively low dosages of 10 to 40 mg/day may be sufficient in some patients. The drug has also shown promise in the treatment of children with severe reflux oesophagitis, in patients with reflux oesophagitis and coexisting systemic sclerosis, and in the prevention of aspiration pneumonia. Evidence suggests that omeprazole is more effective than ranitidine in patients with nonsteroidal anti-inflammatory drug (NSAID)-induced gastric damage who continue to take NSAIDs, especially in patients with large gastric ulcers; however, completion of ongoing studies is required to verify this. (ABSTRACT TRUNCATED AT 400 WORDS)

Publication Types:

- Review
- Review, Tutorial

PMID: 7525198 [PubMed - indexed for MEDLINE]

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☐ 52: Br J Clin Pract Suppl 1994 May-Jun;75:58-61; discussion 62-6 Related Articles, [NEW Books](#), [LinkOut](#)

**Safety of lansoprazole.**

Colin-Jones DG.

Queen Alexandra Hospital, Cosham, Portsmouth.

Publication Types:

- Review
- Review, Tutorial

PMID: 8060803 [PubMed - indexed for MEDLINE]

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☐ 53: Br J Clin Pract Suppl 1994 May-Jun;75:48-55; discussion 56-7 Related Articles, [NEW Books](#), [LinkOut](#)

**Clinical review of lansoprazole.**

Lockhart SP.

Lederle Laboratories, Gosport.

Lansoprazole is an inhibitor of gastric H<sup>+</sup>,K(+) -ATPase, commonly referred to as the 'proton pump'. The pharmacodynamic effect of proton pump inhibition is to reduce gastric acid secretion. Long experience with H<sub>2</sub> antagonists and more recently proton pump inhibitors has demonstrated the value of reducing gastric acid secretion in conditions where acid plays a key role in the pathogenesis of gastrointestinal inflammation and ulceration. The pharmacokinetics, pharmacodynamics and clinical safety of lansoprazole are discussed elsewhere in this supplement, and so this review will focus upon the European and American experience of the efficacy of lansoprazole in the treatment of peptic ulceration and gastro-oesophageal reflux.

Publication Types:

- Review
- Review, Tutorial

PMID: 8060802 [PubMed - indexed for MEDLINE]

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- ☐ 54: Br J Clin Pract Suppl 1994 May-Jun;75:41-5; discussion 46-7 [Related Articles](#), [NEW Books](#), [LinkOut](#)

**Lansoprazole: pharmacokinetics and pharmacodynamics.**

Moules IK.

Lederle Laboratories, Gosport, UK.

**Publication Types:**

- Review
- Review, Tutorial

PMID: 8060801 [PubMed - indexed for MEDLINE]

- ☐ 55: Yale J Biol Med 1994 May-Aug;67(3-4):81-95

[Related Articles](#), [NEW Books](#), [LinkOut](#)

**Gastric acid secretion: activation and inhibition.**

Sachs G, Prinz C, Loo D, Bamberg K, Besancon M, Shin JM.

University of California Los Angeles, USA.

Peripheral regulation of gastric acid secretion is initiated by the release of gastrin from the G cell. Gastrin then stimulates the cholecystokinin-B receptor on the enterochromaffin-like cell beginning a calcium signaling cascade. An exocytotic release of histamine follows with concomitant activation of a C1- current. The released histamine begins the H2-receptor mediated sequence of events in the parietal cell, which results in activation of the gastric H<sup>+</sup>/K<sup>+</sup> - ATPase. This enzyme is the final common pathway of acid secretion. The H<sup>+</sup>/K<sup>+</sup> - ATPase is composed of two subunits: the larger alpha-subunit couples ion transport to hydrolysis of ATP, the smaller beta-subunit is required for appropriate assembly of the holoenzyme. Both the membrane and extracytoplasmic domain contain the ion transport pathway, and therefore, this region is the target for the antiseecretory drugs of the post-H2 era. The 100 kDa alpha-subunit has probably 10 membrane spanning segments with, therefore, five extracytoplasmic loops. The 35 kDa beta-subunit has a single membrane spanning segment, and most of this protein is extracytoplasmic with the six or seven N glycosylation consensus sequences occupied. Omeprazole is an acid-accumulated, acid-activated, prodrug that binds covalently to two cysteine residues at positions 813 (or 822) and 892, accessible from the acidic face of the pump. Lansoprazole binds to cys321, 813 (or 822) and 892; pantoprazole binds to cys813 and 822. The common binding site for these drugs (cys813 or 822) is responsible for the inhibition of acid transport. Covalent inhibition of the acid pump improves control of acid secretion, but since the effective half life of the inhibition in man is about 48 hr, full inhibition of acid secretion, perhaps necessary for eradication of *Helicobacter pylori* in combination with a single antibiotic, will require prolongation of the effect of this class of drug.

**Publication Types:**

- Review
- Review, Tutorial

PMID: 7502535 [PubMed - indexed for MEDLINE]

- ☐ 56: Leber Magen Darm 1994 Mar;24(2):66-8, 71

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**[Lansoprazole--profile of a new proton pump inhibitor]**

[Article in German]

Seifert E.

I. Med. Klinik, Stadt. Krankenhaus Kemperhof Koblenz.

Lansoprazole, a new proton pump inhibitor, selectively inhibits the H<sup>+</sup>/K<sup>+</sup>-ATPase. Its inhibitory effect on basal and gastrin stimulated gastric acid secretion is equal to omeprazole and stronger than that of H2-receptor antagonists. Healing rates concerning gastric and duodenal ulcers and refluxesophagitis are significantly higher compared to H2-receptor antagonists and at least comparable to omeprazole. Regarding pilot studies in *H. pylori* eradication therapy, lansoprazole in combination with various antibiotics is

expected to show good eradication rates. Considering its excellent safety and interaction profile lansoprazole is effective and safe in treating acid related disorders.

Publication Types:

- Review
- Review, Tutorial

PMID: 8196467 [PubMed - indexed for MEDLINE]

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☐ 57: Nippon Rinsho 1993 Dec;51(12):3255-60

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**[In vitro anti-microbial activity against H. pylori and clinical efficacy of various drugs]**

[Article in Japanese]

**Fujioka T, Kawasaki H, Su WW, Nasu M.**

Second Department of Internal Medicine, Oita Medical University.

The in vitro antimicrobial activity against H. pylori and clinical efficacy of various antibiotics and antiulcer drugs are summarized in this study. H. pylori highly sensitive to most of the beta-lactams and macrolides. Especially, amoxicillin and clarithromycin have satisfactory in vitro activity against H. pylori. The anti-ulcer drugs, sofalcon and plaunotol, used in Japan as mucosal protective agents, also have a weak activity against H. pylori with MIC50 12.5 micrograms/ml and MIC90, 50-100 micrograms/ml, while H2-receptor antagonists do not have in vitro activity. Efficacy of antibiotics as monotherapy for eradicating H. pylori is rather poor. The best results with monotherapy are obtained with clarithromycin and amoxicillin. Omeprazole monotherapy suppresses H. pylori infection but does not eradicate H. pylori. Combined therapy with omeprazole and amoxicillin have strong synergistic effects on the eradication of H. pylori (68.8%). Newly developed proton pump inhibitors, such as lansoprazole, E-3810 and their derivatives, showed strong in vitro activity against H. pylori suggesting that these drugs may be useful for the treatment of H. pylori infection.

Publication Types:

- Review
- Review, Tutorial

PMID: 8283643 [PubMed - indexed for MEDLINE]

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☐ 58: World J Surg 1993 Jul-Aug;17(4):468-80

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**Control of gastric acid hypersecretion in the management of patients with Zollinger-Ellison syndrome.**

**Metz DC, Pisegna JR, Fishbeyn VA, Benya RV, Jensen RT.**

Digestive Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892.

During the last 5 years important advances have occurred in the control of gastric acid hypersecretion in Zollinger-Ellison syndrome (ZES). The increased availability of potent gastric acid antisecretory agents such as histamine H2-receptor antagonists and more recently the H<sup>+</sup>K<sup>+</sup>-ATPase inhibitors such as omeprazole and lansoprazole have made it possible to medically control acid secretion in all patients. Increased understanding of the variation in antisecretory drug dosage between individual patients has led to identification of criteria to ensure effective antisecretory control and to the recognition of subgroups of patients who require special monitoring. Effective regimens for parenteral antisecretory control during surgery have been established. The importance of parathyroidectomy in patients with multiple endocrine neoplasia type I with ZES and the possible usefulness of highly selective vagotomy have been investigated. We review here the new data that led to increased understanding in each of these areas from our studies and studies by others.

Publication Types:

- Review
- Review, Academic

PMID: 8362529 [PubMed - indexed for MEDLINE]

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☐ 59: Aliment Pharmacol Ther 1993;7 Suppl 1:56-60, discussion 61-6

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### **Safety of lansoprazole.**

**Colin-Jones DG.**

Queen Alexandra Hospital, Portsmouth, UK.

The care with which patients are monitored during clinical trials provides an excellent database to assess the tolerability and safety of drugs. Additional information can be obtained from knowledge of the compound itself, its metabolism and its pharmacological action. Other compounds from the same class can highlight areas that need particular study. All these factors have been used to assess the safety of lansoprazole. Lansoprazole has been administered to 4749 subjects and has been well tolerated. Only 1.2% of patients have been withdrawn from trials because of suspected drug-related events but there was no pattern and no relationship to drug dosage. Diarrhoea (3.2%) and headache (4.7%) were the most commonly reported adverse events.

#### **Publication Types:**

- Review
- Review, Tutorial

PMID: 8490081 [PubMed - indexed for MEDLINE]

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☐ 60: Aliment Pharmacol Ther 1993;7 Suppl 1:37-40, discussion 61-6

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### **Acute treatment of duodenal ulcer: experience with lansoprazole.**

**Mignon M, Vallot T.**

Department of Hepatogastroenterology, CHU, Bichat and Claude-Bernard Hospital, Paris, France.

Clinical experience with lansoprazole in the acute treatment of duodenal ulcer patients has been compared with treatment using placebo, H<sub>2</sub>-antagonists or omeprazole. Among the various lansoprazole dosage regimens that have been tested, 30 mg daily for 4 weeks appears to be the optimal regimen to relieve pain rapidly and to heal ulceration in up to 90-95% of patients. Lansoprazole tolerability in the short term appears excellent, most adverse effects are trivial and not dose related. Duodenal ulcer relapse after ulcer healing with lansoprazole appears to occur at a rate similar to that observed after treatment with omeprazole or histamine H<sub>2</sub>-antagonists.

#### **Publication Types:**

- Clinical Trial
- Randomized Controlled Trial
- Review
- Review, Tutorial

PMID: 8490078 [PubMed - indexed for MEDLINE]

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☐ 61: Aliment Pharmacol Ther 1993;7 Suppl 1:34-6, discussion 61-6

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### **Lansoprazole in the treatment of reflux oesophagitis: a survey of clinical studies.**

**Berstad A, Hatlebakk JG.**

Department of Medicine, Haukeland University Hospital, Bergen, Norway.

The newly developed proton pump inhibitor lansoprazole has been compared to placebo, ranitidine and with omeprazole in a number of clinical studies in patients with reflux oesophagitis. In three comparative studies against ranitidine, lansoprazole was found to be superior in terms of healing rates and symptom relief. In two studies against omeprazole, no significant difference was found in healing rates, while a Scandinavian study demonstrated more prompt relief from heartburn. Further studies are presently being conducted to



evaluate the potential of lansoprazole in long-term treatment of reflux oesophagitis. It is concluded that lansoprazole is a safe, effective therapy for reflux oesophagitis, superior to ranitidine and comparable with omeprazole.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial
- Review
- Review, Tutorial

PMID: 8490077 [PubMed - indexed for MEDLINE]

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☐ 62: Aliment Pharmacol Ther 1993;7 Suppl 1:4-12, discussion 29-31

[Related Articles](#), [NEW Books](#), [LinkOut](#)

### **The continuing development of gastric acid pump inhibitors.**

Sachs G, Shin JM, Besancon M, Prinz C.

UCLA.

The synthesis and action of H<sub>2</sub>-receptor antagonists changed the understanding of gastric acid secretion as well as changing medical therapy for peptic ulcer disease. It is now known that peripheral regulation of gastric acid secretion depends largely, but not entirely, on histamine release from the enterochromaffin-like cell. There is, therefore, no final common pathway for stimulation of the parietal cell. In contrast, all stimuli converge to activate the acid pump, the H<sup>+</sup>,K<sup>+</sup>-ATPase. Inhibition of this pump by clinically useful drugs was achieved by developing derivatives of timoprazole, pyridyl-2-methylsulfinyl benzimidazole. Two of these derivatives, omeprazole and lansoprazole, have shown superiority in acid control and therefore in therapy for peptic ulcer disease compared to the available H<sub>2</sub>-receptor antagonists.

Publication Types:

- Review
- Review, Tutorial

PMID: 8387826 [PubMed - indexed for MEDLINE]

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☐ 63: Clin Ther 1993;15 Suppl B:22-31

[Related Articles](#), [NEW Books](#), [LinkOut](#)

### **Treatment of patients with Zollinger-Ellison syndrome.**

Mignon M, Pospai D, Forestier S, Vatie J, Vallot T.

Department of Hepato-Gastroenterology, Bichat-Claude Bernard Hospital, Paris, France.

In the treatment of Zollinger-Ellison syndrome patients with severe disease and acid hypersecretion, proton pump inhibitors are the drugs of choice. Data have now been accumulated on lansoprazole treatment of 41 patients (21 treated at the National Institutes of Health [NIH], Bethesda, Maryland, USA, and 20 treated at the Bichat-Claude Bernard Hospital, Paris, France). Short-term studies of the inhibitory action of lansoprazole on acid secretion have been carried out in both institutions. Our group first performed a dose-response analysis of the efficacy of lansoprazole in reducing basal acid output (BAO) in four patients with severe Zollinger-Ellison syndrome (mean BAO 52 +/- 9 [SD] mmol H<sup>+</sup>/h) who had previously been treated with a mean omeprazole dosage of 75 mg/day. The maximum acid inhibitory effect was obtained with lansoprazole 60-90 mg/day. The 40-hour duration of action of lansoprazole appears equivalent to that of omeprazole. In a second study at the Bichat-Claude Bernard Hospital, nine Zollinger-Ellison syndrome patients underwent 24-hour intragastric pH monitoring while receiving lansoprazole (mean dosage 80 mg/day, range 30-165 mg/day) or omeprazole (mean dosage 75 mg/day, range 20-180 mg/day). The acid inhibitory activity of the two drugs was comparable. Those patients are currently receiving long-term maintenance treatment with lansoprazole, and satisfactory clinical and biological secretory control has been achieved. The long-term safety and efficacy of lansoprazole administration were studied in the 21 patients followed at the NIH. In those patients the initial maintenance dose was determined using acid inhibition studies; in all patients lansoprazole controlled gastric acid hypersecretion and peptic symptoms in both the short and long term. The mean initial maintenance dose was 60 mg QID, except for two patients who required 60 mg BID. During long-term treatment (mean duration 31 months, range 1-43 months), six patients required a dosage increase within the first year,

while the lansoprazole dose could be reduced in six others. The safety profile of lansoprazole has been excellent. Comparable results have been noted in nine Zollinger-Ellison syndrome patients during an ongoing evaluation in our institution. These studies indicate that lansoprazole is an efficacious, well-tolerated antisecretory agent in patients with Zollinger-Ellison syndrome.

Publication Types:

- Review
- Review, Tutorial

PMID: 8205592 [PubMed - indexed for MEDLINE]

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☐ 64: Clin Ther 1993;15 Suppl B:2-13

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**Treatment of gastroesophageal (acid) reflux with lansoprazole: an overview.**

Dobrilla G, Di Fede F.

Division of Gastroenterology, General Regional Hospital, Bolzano, Italy.

Despite the fact that reflux esophagitis is a multifactorial disease, inhibition of gastric acid secretion is the mainstay of medical treatment, both for moderate and severe cases. Antisecretory agents lower the acidity of the refluxate, thus decreasing its aggressive effect, which favors the mucosal healing process. The greater the acid inhibition, the greater will be the mucosal repair. This is the reason for a therapeutic gain for H2-receptor antagonists over anticholinergics and antacids, and for proton pump inhibitors over H2-receptor antagonists. The most recently developed proton pump inhibitor, lansoprazole, at doses of 15, 30, or 60 mg/day for 4 and 8 weeks of treatment, has proven to be significantly more effective than placebo (one multicenter study involving 292 patients) or ranitidine (three multicenter studies involving 653 patients) in terms of mucosal healing and symptom relief. In two comparative trials with omeprazole 20 mg vs lansoprazole 30 mg (in a total of 349 evaluable patients) healing rates were found to be similar, but in one trial the relief of heartburn proved to be significantly more pronounced in patients receiving lansoprazole who also used fewer antacids. The frequency of adverse events was comparable in the two treatment groups. Reflux esophagitis is a chronic condition and after stopping antisecretory treatment, including lansoprazole, most patients relapse in terms of symptoms and endoscopic lesions, which suggests the need for long-term treatment. However, a strategy for long-term control of reflux esophagitis remains to be defined (lower daily dose, alternate-day standard dose, or concomitant prokinetic drugs?). The safety of proton pump inhibitors given for prolonged periods also needs to be more thoroughly evaluated.

Publication Types:

- Review
- Review, Tutorial

PMID: 7911400 [PubMed - indexed for MEDLINE]

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☐ 65: Drugs 1992 Aug;44(2):225-50

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**Lansoprazole. A review of its pharmacodynamic and pharmacokinetic properties and its therapeutic efficacy in acid-related disorders.**

Barradell LB, Faulds D, McTavish D.

Adis International Limited, Auckland, New Zealand.

Lansoprazole is an effective acid pump inhibitor acting at the final enzymatic step of the acid secretory pathway of the parietal cell, decreasing gastric acid secretion regardless of the primary stimulus. Results of short term (less than 8 weeks) clinical trials have shown lansoprazole to be significantly superior to placebo and ranitidine in the treatment of duodenal ulcer, both in the rate of healing and in overall healing at 4 weeks. Lansoprazole appears to heal duodenal ulcer more quickly than famotidine, and demonstrates slightly greater efficacy at 4 weeks, although both drugs appear to have equivalent efficacy overall. Gastric ulcers and reflux oesophagitis are also healed by lansoprazole 30 mg/day for 4 to 8 weeks, with healing rates after 8 weeks of approximately 85 to 95% for both indications. Lansoprazole appears to be superior to ranitidine and comparable to omeprazole in treating reflux oesophagitis. Furthermore, lansoprazole has relieved reflux symptoms more quickly than either ranitidine or omeprazole. Preliminary data also indicate that lansoprazole may be effective in the treatment of peptic ulcer disease and reflux oesophagitis refractory to

H2-receptor antagonists, and in patients with Zollinger-Ellison syndrome. While direct comparisons with omeprazole are limited, results suggest that lansoprazole, used for short term treatment, is at least as effective as omeprazole in the treatment of peptic ulcer and reflux oesphagitis. Lansoprazole has been well tolerated in short term clinical trials, with an incidence of adverse effects comparable with that of other agents in its therapeutic class. Trials assessing long term tolerability data are ongoing and will be required as part of the assessment of the safety profile, if lansoprazole is to be used prophylactically to prevent ulcer recurrence. Thus, by virtue of its ability to heal ulcers and rapidly relieve associated symptomatology, lansoprazole represents a useful alternative for the treatment of acid related disorders.

Publication Types:

- Clinical Trial
- Multicenter Study
- Review
- Review, Tutorial

PMID: 1382017 [PubMed - indexed for MEDLINE]

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☐ 66: South Med J 1991 Sep;84(9):1078-87

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**Proton-pump inhibition for acid-related disease.**

Holt S.

Department of Medicine, School of Medicine, University of South Carolina, Columbia 29203.

Omeprazole and lansoprazole are the forerunners of a group of substituted benzimidazole compounds that block the gastric proton pump. These drugs exert a potent antisecretory effect by blocking the final common pathway of acid secretion. Prolonged, potent reduction of acid secretion using omeprazole has resulted in significant therapeutic advantage over existing antisecretory medication, such as H2 receptor antagonists (H2RAs). Research experience with lansoprazole indicates that it has treatment properties for acid-related disease that are similar to those of omeprazole. Omeprazole has been used successfully in the treatment of reflux esophagitis and the Zollinger-Ellison syndrome in the United States over the past year and has received approval recently as first-line therapy for duodenal ulcer disease. Research involving more than 20,000 individuals, postmarketing surveillance studies, and thorough safety studies in man and animals have shown omeprazole to be well tolerated, with an incidence and spectrum of adverse events in clinical trials similar to those observed with H2RAs.

Publication Types:

- Review
- Review, Tutorial

PMID: 1653998 [PubMed - indexed for MEDLINE]

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